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TABLE *of* CONTENTS

Steroids in Infection
RALPH TOMPSETT, M.D. 173

Use and Abuse of X-ray Therapy for Benign Skin Conditions, With Particular Reference to X-ray Atrophy
DONALD M. PILLSBURY, M.D. 180

Severe Toxemia of Pregnancy
MILTON L. MCCALL, M.D. 188

Office Diagnosis of Congenital Malformations of the Heart, Part 2
BENJAMIN M. GASUL, M.D., RENE A. ARCILLA, M.D. AND MAGNUS H. AGUSTSSON, M.D. 191

Primal Anxiety and Psychiatric Emergencies
H. KEITH FISCHER, M.D. AND BARNEY M. DLIN, M.D. 200

Prolapse of the Uterus and Vagina
LAMAN A. GRAY, M.D. 207

Management of the Child With Nasal Allergy
GEORGE B. LOGAN, M.D. 217

Diabetic Neuropathy
KENDRICK SMITH, M.D. 223

Campaign for Detecting Cervical Cancer
KURT BOCHNER, M.D. 229

(Continued on page A-4)

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Medical Color Photography Simplified
BEN R. WILTBERGER, M.D. 274

SYMPOSIUM

Effect of Drugs on the Gastrointestinal Tract
ROBERT M. ZOLLINGER, M.D., WILLIAM D. DAVIS, JR., M.D. AND ANTHONY R. CURRERI, M.D. 234

NUTRITION

Obesity, Drugs and Formula Diets
SAMI A. HASHIM, M.D. 245

CLINICOPATHOLOGIC CONFERENCE

Osteolytic Lesions and Cardiac Failure
FROM THE VETERANS ADMINISTRATION HOSPITAL, HINES, ILLINOIS 251

CLINICAL STUDY

Guanethidine in the Treatment of Hypertension
ALBERT N. BREST, M.D., RYUICHI KODAMA, M.D., FRANK NASO, M.D. AND JOHN H. MOYER, M.D. 260

SCIENTIFIC EXHIBIT

Esophageal Diverticulum
DAVID P. BOYD, M.D. AND ROBERT E. WISE, M.D. 265

PHYSICAL MEDICINE AND REHABILITATION

Self-help Devices: Homemaking: Opening Containers
EDWARD W. LOWMAN, M.D. AND HOWARD A. RUSK, M.D. 272

DEPARTMENTS

EDITORIALS 280
Progress in Military Medicine
Women in Industry
Doctors' Choice

FORTHCOMING FEATURES A-9

(Continued on page A-6)

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PROBLEMS AND SOLUTIONS A-26
Thio-TEPA
Diffuse Vascular Disease
Scoliosis
Excessive Thirst
Clinodactyly

WHAT'S HAPPENING IN MEDICINE ..... Facing A-32

LABORATORY NOTES A-36
Pure Water, Part 1
DOUGLAS A. NELSON, M.D.

FORENSIC MEDICINE A-62
Chemical Poisoning in an Urban Area
IRVING SUNSHINE, PH.D.

MEETINGS AND POSTGRADUATE COURSES A-72, 233

RADIOLOGY A-77
Small Hiatus Hernia, Gastroesophageal Regurgitation and the Phrenic Ampulla
FREDERIC E. TEMPLETON, M.D.

MEDICINE FROM ABROAD A-87

NEW FOR YOUR ARMAMENTARIUM A-102

GREAT NAMES IN AMERICAN MEDICAL HISTORY A-118
Ferdinand R. Schemm, M.D., Montana

YOUR FINANCES A-129
Financial Planning for the Medical Practitioner

THE MEDICAL BOOKMAN A-142

THE MEDICAL MUSE. Richard Armour A-146

DR. PEPYS' PAGES. Morris Fishbein, M.D. A-162

INDEX TO TECHNICAL EXHIBITS A-177

FORTHCOMING FEATURES

IN Postgraduate Medicine

Hypoventilation

GEOFFREY L. BRINKMAN, M.D., Henry Ford Hospital, Detroit

Coccidioidomycosis: A Primer

MARCO BRUSCHI, M.D., Bakersfield, California

Acute Urinary Retention

DAVID A. CULP, M.D., State University of Iowa College of Medicine, Iowa City

Common Causes of Disturbed Nasal Function

KENNETH H. HINDERER, M.D., University of Pittsburgh School of Medicine, Pittsburgh

Congestive Heart Failure; Its Physiopathology and Treatment

WILLIAM H. MORSE, M.D. AND RICHARD J. BING, M.D., Wayne State University College of Medicine, Detroit

Indications for Surgery in Cerebrovascular Accidents

JOHN SHILLITO, JR., M.D., Harvard Medical School, Boston

The Differential Diagnosis of Jaundice

EDWARD H. STORER, M.D., University of Tennessee College of Medicine, Memphis

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1. Beckman, H.: *Pharmacology: The Nature, Action and Use of Drugs*, 2nd Ed. W. B. Saunders Company, Philadelphia and London, 1961, p. 673.

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Problems and Solutions

Readers are invited to submit questions relating to problem cases. Inquiries will be answered by qualified consultants and replies forwarded by mail immediately. Selected problems and solutions are published each month in this section.

• THIO-TEPA

The Editors have received supplemental information regarding inquiries on the use of thio-TEPA, which was mentioned in this section in the June issue of POSTGRADUATE MEDICINE. Detailed information and literature on thio-TEPA are available on request to: Medical Advisory Department, Lederle Laboratories, Pearl River, New York.

• DIFFUSE VASCULAR DISEASE

P. In September 1959, a 59 year old man had a thrombosis in the central vein of the retina of the left eye; multiple hemorrhages completely covered the posterior pole. At that time the prothrombin level was 30 per cent higher than normal. A similar thrombosis had occurred in the right eye in 1953; vision in this eye is now 4/10. In December 1958, the patient had a posterolateral infarct of the left ventricle of the heart; it was of mild evolution with no complications.

At present the patient's pulse is normal, the blood pressure is 150/100, and the cholesterol level is normal. He has been receiving anticoagulant therapy since September 1959, including vitamin E, LUFA® and METHISCHOL®; improvement has been negligible.

What is your opinion on the use of FIBROLYSIN® alone or as a supplement to the treatment described in this case? Can you suggest any additional therapy?

M.D.—Chile

S. It is obvious that this patient has diffuse vascular disease, since bilateral thrombosis of the central veins of the retina and myocardial infarction have occurred. In general, the treatment employed for the myocardial infarction has been excellent; the addition of Fibrolysin would be of no significant value.

The use of anticoagulant therapy with or without Fibrolysin in thrombosis of the central veins of the retina is controversial; in my opinion neither anticoagulant therapy nor Fibrolysin would be effective for this condition.

• SCOLIOSIS

P. A patient with scoliosis of the lumbar part of the spine was detained in ghettos and concentration camps from her twelfth to her sixteenth year, and was forced to do hard labor. She has pain in the lower back and on flexion of the right thigh.

Would it be reasonable to assume that the scoliosis was caused by insufficient nourishment and vitamin deficiency or by late rickets during her detention? Is there any way to differentiate congenital, idiopathic and rachitic scoliosis?

M.D.—New York

S. It is possible that the basic scoliosis was increased by inadequate nutrition and undue physical labor. A mechanical cause of the scoliosis could certainly be worsened by any metabolic process which would ultimately soften or compromise the structural integrity of the bone.

It is possible to distinguish between congenital and idiopathic scoliosis only if evidence of congenital musculoskeletal anomalies is implicated in the diagnosis. Nutritional deficiency could be considered a contributory cause of scoliosis only if there is a proved diagnosis of rickets in childhood and if a definite relation between the rickets and the onset of scoliosis can be established.

(Continued on page A-29)

THERAPEUTIC INDEX

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Patients already receiving other anticonvulsants—Adults and Children (over 8 years): 0.25 Gm. daily, and gradually increased while the dosage of the other drug(s) is gradually decreased. Continued until satisfactory dosage level is achieved for combination, or until other medication is completely withdrawn. *Children under 8 years:* Initially one-half the adult dose, or 0.125 Gm. daily. Gradual increases and decreases as described in adult regimen. (Where a smaller starting dose is required, use 50 mg. tablet.)

When therapy with "Mysoline" alone is the objective, the transition should not be completed in less than two weeks.

Precautions: Side reactions, when they occur, are usually mild and transient, tending to disappear as therapy is continued or as dosage is adjusted. Commonly reported side effects are drowsiness, ataxia, vertigo, anorexia, irritability, general malaise, nausea and vomiting. No serious irreversible toxic reactions have been observed. (Occasionally, megaloblastic anemia has been reported in patients on "Mysoline." The condition is readily reversible by folic acid therapy, 15 mg. daily, while "Mysoline" is continued.) As with any drug used over prolonged periods of time, it is recommended that routine laboratory studies be made at regular intervals.

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• EXCESSIVE THIRST

P. A three year old girl drinks a tremendous amount of water, even waking two or three times a night for this purpose. There is no nocturia. She eats only if forced to do so, has gradually lost weight, and has constipated bowel movements every two days. Her height is 38 in., weight 27¼ lb., and hemoglobin 65 per cent (Tallqvist scale); results of urinalysis, Mantoux test and chest x-ray are negative. Differential count shows abnormal basket cells. The fasting blood sugar and basal metabolic rate have not yet been determined.

What are the diagnosis and treatment?

M.D.—Michigan

S. Excessive desire for water in a three year old child may result from diabetes mellitus, diabetes insipidus or renal disease. The constipation probably is caused by incipient dehydration associated with excessive loss of water in the urine.

Diabetes mellitus usually is accompanied by an increase in appetite, although this is not necessarily true in a three year old child. Diabetes insipidus may be associated with reticuloendotheliosis or lesions of the central nervous system, or it may be of unknown cause. Renal insufficiency generally is insidious in onset, and may be the result of cystinosis, chronic pyelonephritis or other less frequently encountered types of renal tubular insufficiency.

It is difficult to indicate treatment, since the information provided does not permit the establishment of a diagnosis.

• CLINODACTYLY

P. A 15 year old girl has clinodactyly to a moderate degree. What treatment would you recommend for this condition?

M.D.—Nova Scotia

S. Clinodactyly is not particularly uncommon and often has a hereditary basis. Surgical correction is not recommended unless the curvature is more than 40 degrees. Operation on the joint itself generally does not result in improvement and may even cause additional impairment of extension. When the deflection is severe, osteotomy to straighten the finger to an only slightly curved position may be done. However, the cases in which surgical treatment is justified are extremely rare.

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1. Wein, A. B.; The Use of Carisoprodol (SOMA) in Orthopedic Surgery and Rehabilitation, Miller, James G., ed., Wayne State University Press, Detroit, Michigan, 1959.

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What's happening in Medicine ?

POSTGRADUATE MEDICINE'S REPORT of late news of interest to practicing physicians

RADIOIODINE FOR CARDIAC PATIENTS

Society of Nuclear Medicine, Pittsburgh:

• Hypometabolism produced by dosages of iodine 131 has benefited patients with severe angina pectoris, congestive heart failure, and paroxysmal arrhythmia. In a study of 1,068 patients treated in more than 100 cooperating clinics, 80 per cent of those with intractable angina pectoris had excellent or good results. Eighty per cent of 190 patients with recurrent attacks of paroxysmal arrhythmia and 70 per cent of 452 patients with congestive heart failure also showed similar results after six months of therapy. About 50,000 rads to the thyroid was necessary to suppress function.—Dr. H. L. Blumgart, Harvard Medical School, Boston.

• Malignant serous effusions were palliated in 90 per cent of 123 patients by intracavitary instillation of radioactive yttrium. Since yttrium has a strong affinity for proteins, it was combined with human serum albumin. In about 75 per cent of the patients, there was an essentially complete resolution of the effusion after a single treatment.—Dr. Joseph Greenberg, New York Polyclinic Hospital, New York.

ASYMPTOMATIC ARTERIAL STENOSIS

American Neurological Association, Atlantic City:

• A high incidence of stenotic vascular disease of the extracranial arteries was found in individuals without clinical symptoms before death. In vivo cerebral angiography was simulated by injecting an opaque dye mixture into the subclavian and common carotid arteries on both sides. Specimens then were fixed with formalin perfusion. This distends the arterial lumen. Angiographic study of 100 patients showed stenosis of one or more vessels in 25 per cent.—Dr. Bennett Stein, Columbia University College of Physicians and Surgeons, New York.

• Preliminary studies of a device for measuring intracranial blood pressure in the circle of Willis and for monitoring cerebral blood have shown these procedures to be as important as measuring brachial arterial pressure in managing hypertension. The apparatus was basically designed for obtaining plethysmograms of the ophthalmic artery, which is a branch of the internal carotid artery and the circle of Willis.—Dr. Melvin W. Thorner, University of Pennsylvania School of Medicine, Philadelphia.

Thyroid and emotions

World Congress of Psychiatry, Montreal:

• Hypothyroid patients may manifest emotional symptoms rather than typical placid behavior. Twenty-four patients with this disorder showed symptoms similar to those of neurotics, including nervousness, irritability, vehement reactions and a tendency to be easily provoked. Whereas the neurotic blames others for his maladjustment, the patient with a thyroid deficiency takes full responsibility for his behavior. Following treatment with desiccated thyroid, the symptoms usually disappeared.—Dr. Martha Schon, Sloan-Kettering Institute for Cancer Research, New York.

• A history of complications before or during birth was found in 86 per cent of 286 children diagnosed as schizophrenic or as having other neurologic deficits. One-half of the girls and two-thirds of the boys were first-born or second-born children.—Dr. Lauretta Bender, Creedmoor State Hospital, New York.

Drug attacks systemic fungus

American Thoracic Society, Cincinnati:

• The antibiotic X-5079C appears active against disseminated histoplasmosis and blastomycosis. Administered subcutaneously, the drug produces no hematologic, renal or cardiac dysfunction. BROMSULPHALEIN® retention increases, reaches a plateau, and falls rapidly to pretreatment levels when administration of the drug is stopped.—Dr. John P. Utz, National Institutes of Health, Bethesda.

Weather and arthritis

American Rheumatism Association, New York:

• Although it is commonly believed that weather changes affect arthritis, experimental studies on patients who lived continuously in a climate chamber for four weeks revealed that no single factor had any constant effect on the arthritic symptoms or the subjective feelings of the patients. Falling barometric pressure alone did not cause consistent fluid retention, nor did rising pressure produce significant diuresis. Increased physical exertion invariably led to increased symptoms and signs of arthritis on the following day.—Dr. Joseph Lee Hollander, University of Pennsylvania School of Medicine, Philadelphia.

• Epsilon-aminocaproic acid (EACA) may join aspirin and the steroids as a new anti-inflammatory agent. EACA acts on the fibrinolytic system believed to be involved in the mechanism of inflammation. It blocks the activation of plasminogen into plasmin. While this approach has not yet yielded conclusive results in treating rheumatoid arthritis, preliminary indications are that it is effective in progressive systemic sclerosis. It may be an important research clue for the study of connective tissue disease.—Dr. Jerome Rotstein, Montefiore Hospital, New York.

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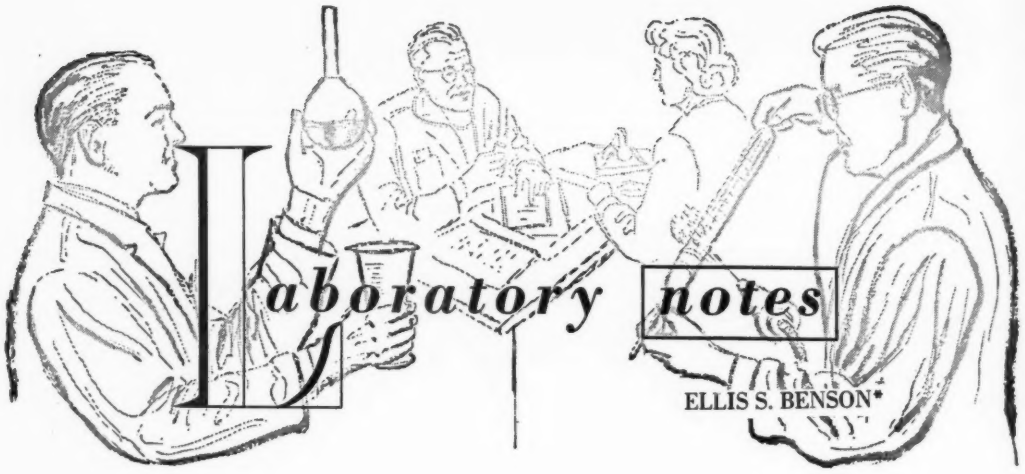

Pure Water, Part 1

DOUGLAS A. NELSON

University of Minnesota Medical School, Minneapolis

Undoubtedly, every laboratory has problems from time to time which are the direct result of contaminated laboratory water thought to be pure. The term "distilled water" has been replaced by a more comprehensive one, "purified water," which includes water purified by de-ionization and water purified by distillation.

In this and next month's columns, Dr. Douglas A. Nelson, instructor in laboratory medicine, University of Minnesota Medical School, discusses differences between distilled and de-ionized water, relative advantages and disadvantages of each, and typical hazards to the quality of laboratory work resulting from impure "purified" water.—Ellis S. Benson, M.D.

RARE indeed is the laboratory which has not had some kind of problem with the purity of its water. Knowledge of the factors involved in obtaining and maintaining pure water then attains real value. This presentation is not a comprehensive review, but it includes some of these factors, a comparison of the two major methods of water purification, and a discussion of some problems encountered if laboratory water is impure.

DOUGLAS A. NELSON

Methods of Purification

Beginning with the fifteenth edition of "The Pharmacopoeia of the United States of America,"[1] the entry "Purified water" replaced that of "Distilled water," with the stipulation that purified water is obtained by either distillation or de-ionization. Prior to either of these processes, pretreatment of water is required, which may include sedimentation, coagulation, filtration, aeration or chlorination.[2] These processes will not be discussed here, as they are usually the function of the municipal water treatment plant. It may be helpful

(Continued on page A-38)

*Director of Hospital Laboratories and Associate Professor of Clinical Laboratory Medicine and of Pathology, University of Minnesota Medical School, Minneapolis, Minnesota.

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to know, however, the composition of laboratory tap water, particularly regarding hardness ingredients, i.e., calcium and magnesium salts. Many public water supplies reduce the hardness of ground water supplies to 70 to 100 parts per million (ppm) calcium carbonate equivalents. There are 1 to 60 ppm in soft water.[3]

The area of our concern is the purification of tap water for suitability in biologic testing, bacteriologic studies, tissue culture work, biochemical analyses, etc. The methods of purification to be considered are distillation and de-ionization.

Distillation—Distillation is the process of vaporizing a liquid and collecting the vapor by condensation, leaving the contaminants behind. Theoretically, this should result in perfectly pure water. Practically, however, the fact that water is distilled is not a guarantee that it is pure. Kolthoff and Sandell[4] discussed some of the sources of impurities.

1. Substances may be dissolved from apparatus or containers. The amount of this type of contamination will depend on the composition of the condensers and of the containers used for storage. Copper is a frequent contaminant. Even glass is not completely satisfactory, because the alkaline constituents of glass slowly dissolve in water.[4,5]

2. Dissolved materials in the feed water may be carried over into the distillate. Several factors important here were discussed in a detailed study by Shotton and Habeeb.[6] The term "entrainment" designates a phenomenon in which a small proportion of the feed liquid is carried as droplets by the vapor into the condenser. Shotton and Habeeb found that, in general, contamination by entrainment increased with (1) increasing diameter of the stillhead* and (2) increasing rate of distillation with streamline or laminar flow of vapor. When the vapor flow became turbulent with higher rates of distillation, the entrainment decreased due to contact of the droplets with the walls of the stillhead. At still higher rates of distillation, the entrainment increased sharply due to a film of liquid climbing up the walls of the stillhead and spilling over into the condenser, a phenomenon called "gross carry-over." As might be expected, when the length of the stillhead was increased, the entrainment decreased. Thus, these authors showed the importance of the design of distillation apparatus and of rates of distillation in obtaining water of high purity.

To prevent entrainment, commercial stills are usually provided with a mechanical device such as the Spanish prison baffle of the Barnstead still. Recognizing that entrainment or carry-over is the chief source of pyrogens in distilled water, the "British Pharmacopoeia" directs that in production of water for injection the still must be fitted with an efficient device to prevent entrainment.[6] Gross carry-over can be prevented by providing a hot spot in the stillhead, thus breaking up the rising film of liquid.[7]

3. Dissolved gases, especially carbon dioxide, can be troublesome. Gayer and Woontner[8] found that water redistilled from an alkaline solution of permanganate was of pH 5.5 to 5.7, due to equilibrium solubility of atmospheric carbon dioxide. These authors did not find that boiling the distilled water and cooling it under an inert atmosphere would completely free it of carbon dioxide; the resulting pH was 5.8 to 6.2. However, purging the water with carbon dioxide-free air for several hours did remove the carbon dioxide. By performing a redistillation from a dilute solution of a nonvolatile acid under carbon dioxide-free nitrogen and finally flushing the water with purified hydrogen, they consistently obtained water of pH 6.9 to 7.2 at 25° C.

A suggested procedure for good distilled water is to carry out an initial distillation from alkaline permanganate in order to oxidize organic material and a second distillation from dilute sulfuric acid to remove the last traces of ammonia, amines and other basic material.[4,9] The distillate must, of course, be protected from the atmosphere and stored in a suitable container.

De-ionization—The book of Exodus records the story of the flight of Moses and the chil-

(Continued on page A-40)

*The stillhead is the vertical column connecting the flask containing the boiling liquid to the top of the condenser.

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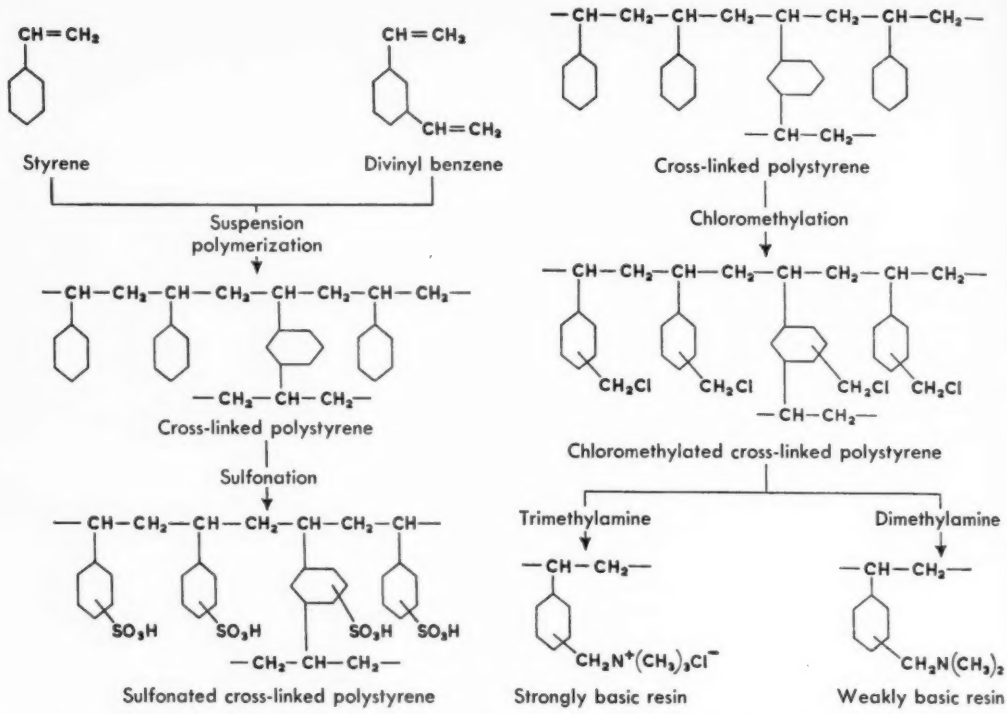


FIGURE 1. Preparation of strongly acidic cation exchange resin (*left*) and of anion exchange resins (*right*).
(Reprinted with permission from Pepper, K. W. and Hale, D. K.[12])

dren of Israel out of Egypt. After the waters of the Red Sea had engulfed Pharaoh's army, the Israelites spent three days in the wilderness of Shur and found no water. "And when they came to Marah, they could not drink of the waters of Marah, for they were bitter . . . . And the people murmured against Moses, saying, 'What shall we drink?' . . . and the Lord showed him a tree, which when he had cast into the waters, the waters were made sweet." A recent exegesis suggests a natural cause of this seeming miracle, namely, ion exchange. The oxidized cellulose of the tree may have entered into an exchange reaction with the bitter electrolytes of the water, making the water potable.[10]

Ion exchange is the "reversible exchange of ions between a solid (the resin) and a liquid in which there is no substantial change in the structure of the solid."[11] The phenomenon of ion exchange has been known for over a century, but the mechanism was elucidated only with the development of synthetic ion exchange resins in 1935.

The most successful of current resins is polystyrene, which is cross-linked for stability with divinyl benzene (figure 1). Sulfonic groups are attached to this skeleton to form a strongly acidic resin (cation exchange resin). Cations in water passing through the resin will exchange with the hydrogen ion of the sulfonic groups ($-SO_3H$).

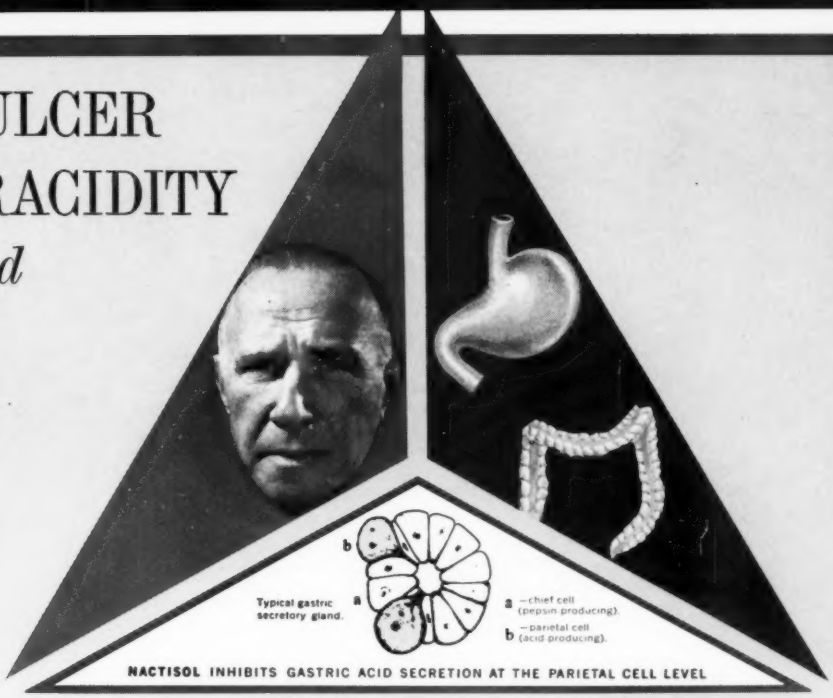
1. $$Na^+ + H\cdot resin \underset{\text{regeneration}}{\overset{\text{treatment}}{\rightleftharpoons}} Na\cdot resin + H^+$$

The relative replacing power generally follows the lyotropic series:

2. $Li^+ < Na^+ < K^+ < Rb^+ < Cs^+ < Mg^{++} < Ca^{++} < Sr^{++} < Ba^{++}$ etc.

(Continued on page A-42)

N PEPTIC ULCER
AND HYPERACIDITY
with associated
tension and
nervousness



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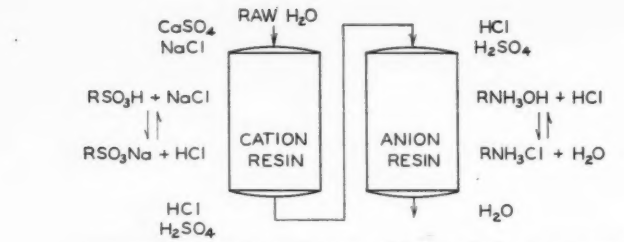

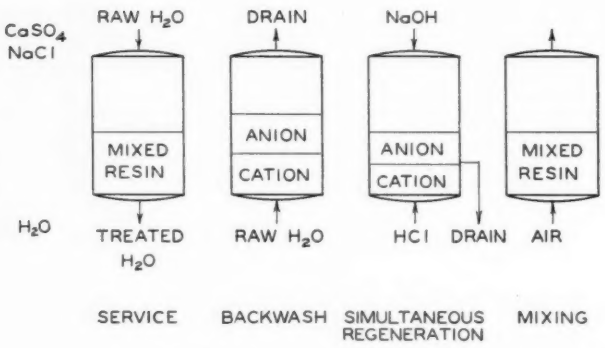

FIGURE 2. Technics of de-ionization.

The position of H^+ in this series will depend on the strength of the acidic group; for sulfonic acid, H^+ is about the same as lithium.

Anion exchange resins are formed by treating a chloromethylated polystyrene with a tertiary amine to form a strongly basic resin or with a primary or secondary amine to form a weakly basic resin (figure 1).[12] Polymeric amines of the weak base resin are thought to behave in aqueous solutions in a manner similar to soluble amines.[10]

3. $RNH_2 + H_2O \rightleftharpoons RNH_3^+ + OH^-$

The quaternary amines of the strong base resin are charged with hydroxyl ions when the resin is treated with sodium hydroxide, as in the regeneration phase of reaction 4. Anions in the water passing through the resin then will exchange with the substituted hydroxyl ions on the amine.

4. $Cl^- + \text{resin}\cdot OH \underset{\text{regeneration}}{\overset{\text{treatment}}{\rightleftharpoons}} \text{resin}\cdot Cl + OH^-$

The relative replacing power for anions follows the series:

5. OH^- (of strong base) $< F^- < Cl^- < Br^- = I^- = Ac^- < MoO_4^= < PO_4^{\equiv} < AsO_4^{\equiv} < NO_3^- <$ citrate $<$ chromate $< SO_4^= = OH^-$ (of weak base)

If raw water is passed first through a column containing beads or granules of a cation exchange resin and then through an anion exchange resin, one perceives by combining equations 1 and 4 that pure water will be generated as cations and anions are removed by the resins. A particle of water reaches the bottom of the column by (1) passing through the interstitial bead lattices, (2) leakage between beads, or (3) leakage between the column and the beads. Obviously, only the first-mentioned is effective in purifying water, and the design of the column and the particle size and shape thus assume importance.[13]

The degree of cross linkage in the resin can be varied by changing the concentration

(Continued on page A-44)

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*Cass, L. J.: Canad. M.A.J. 84:1114 (May 20) 1961.

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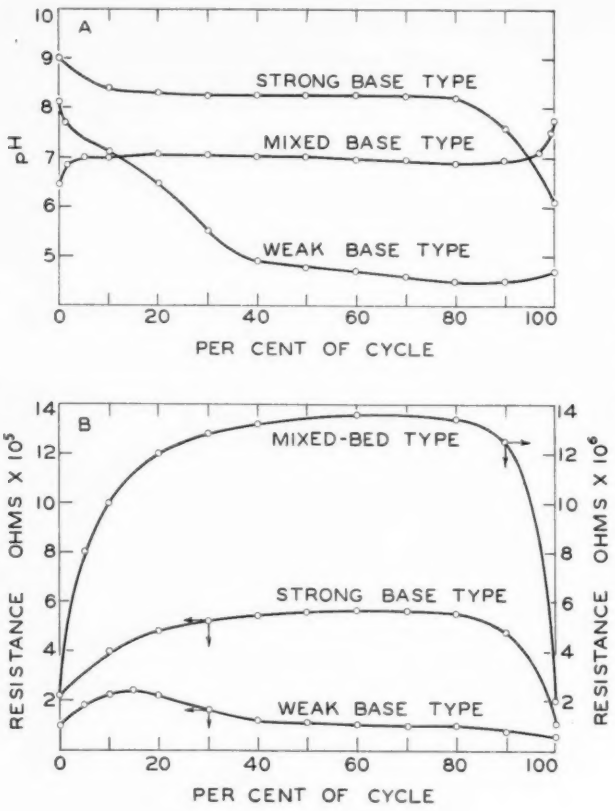

FIGURE 3. The pH (*top*) and resistance (*bottom*) of de-ionized water as a function of per cent of operational cycle for three types of de-ionizing units.

(Reprinted with permission from Reents, A. C. and Wantz, J. F.[15])

of the cross-linking agent divinyl benzene. A higher degree of cross linking will produce a resin with lower permeability, lower equilibrium rate, decreased ability to accommodate large ions, higher capacity, and increased physical stability.[14]

Two technics are commonly used to achieve contact between the water and the resin (figure 2). In conventional (two bed) de-ionization, the raw water passes first through a cationic resin and then through an anionic resin. When the conductivity* of the effluent water rises past the desired level, indicating exhaustion of available sites on the resin and increasing ionic impurity of the treated water, the resins must be regenerated. First, tap water is flushed through the resin in the reverse direction (backwash). Then a strong acid is run through the cationic resin and a strong base through the anionic resin, reversing reactions 1 and 4 and recharging the resins with hydrogen and hydroxyl ions. In mixed-bed de-ionization, both the cationic and anionic resins are in the same column. This combination has been made possible by the invention of strong base synthetic resins which are less dense than cation exchange resins. After the backwashing with tap water, the resins separate and simultaneous regeneration of both is possible in one tank (figure 2).

Mixed-bed de-ionization is more efficient than conventional de-ionization, since it is the equivalent of many de-ionizers in one vessel.

(Continued on page A-46)

*Conductivity is a measure of the ability of a solution to conduct an electric current. It varies with the concentration of ions and the velocities of those ions in an electric field. Ionically pure water will have a high resistivity (resistance) and a low conductivity. Conductivity is measured by an electronic instrument incorporating a Wheatstone bridge.

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Figure 3 illustrates some of the differences in purity of water from two bed de-ionizers of strong base, weak base and mixed-bed types. As 100 per cent of the cycle is approached, the resin is reaching exhaustion. The pH of water from the mixed-bed de-ionizer is neutral. That from the strong base type is slightly basic due to some residual sodium hydroxide from the anionic resin. The gradual drop in pH of water from the weak base type is due to increasing carbon dioxide in the effluent, which the resin cannot adequately remove. The resistance of the water from the mixed-bed type is far higher,[15] indicating a lower ion content.

While water which has a high resistance or very low conductivity can be obtained from mixed-bed ion exchange, water which has stood for some hours in a mixed bed shows a relatively high conductivity. This is thought to be due to colloidal polyelectrolytes released by the resins which, because of their size, are unable to penetrate into resin particles of the opposite charge.[16] Thus, the purity in this respect will depend on the duration of contact with the resins. Rapid flow through a short column may allow electrolytes in the feed water to break through, while slow flow through a long column may introduce organic polyelectrolytes into the water.

Comparison of Distillation and De-ionization

In essence, purification of water by distillation is removal of the water from the impurities; purification by de-ionization is removal of the impurities from the water. Thus, it can be seen that distillation is relatively expensive, with heavy power costs because of the high specific heat and latent heat of evaporation of water. The cost of the essential regular cleaning of the still is also significant. On the other hand, de-ionization is relatively inexpensive, with no power costs. The major costs are the resins and the regenerating solutions. Although resins are costly, their life spans are long enough to make them economically practical.[10]

By nature, distilled water is sterile, but de-ionization does not necessarily sterilize water. Distilled water is theoretically free of all impurities, while de-ionization itself does not remove colloidal or other nonionic impurities; their removal depends on the filtering action of the resin and hence on the physical characteristics of the particles.

Comparison of the efficiency of removing various contaminants will, of course, depend on the specifications of the individual apparatus for distillation and for ion exchange, and general comparison has little meaning. Specific studies with regard to common contaminants will be discussed in next month's column, with consideration of common difficulties due to contamination of supposedly pure water.

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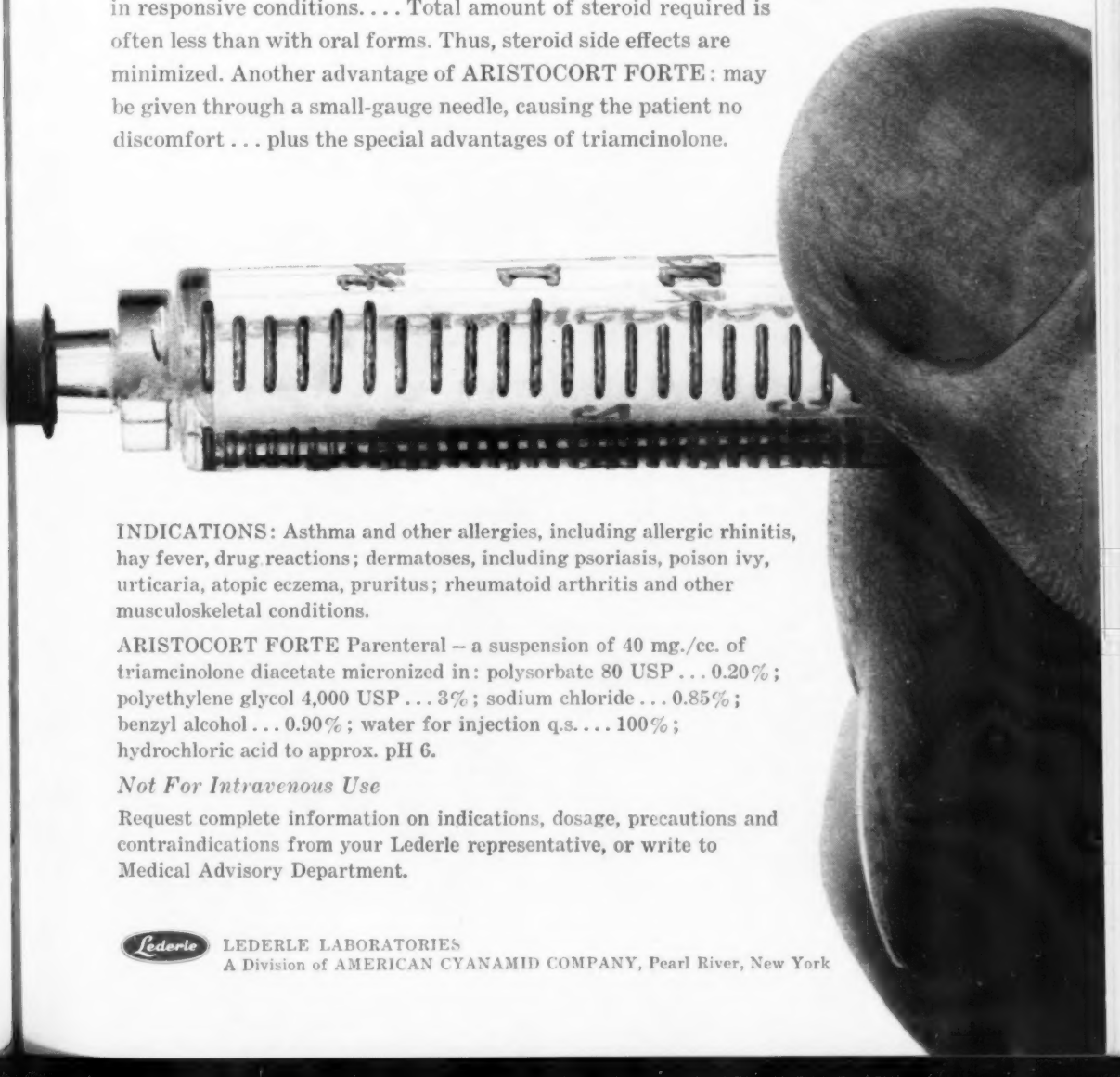

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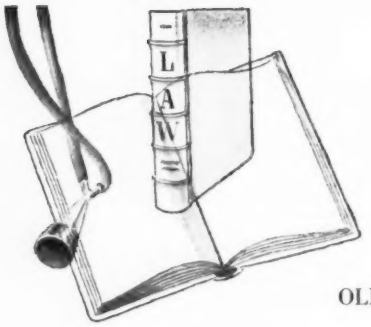

Forensic Medicine

OLIVER C. SCHROEDER, JR.*

Chemical Poisoning in an Urban Area

IRVING SUNSHINE†

Western Reserve University School of Medicine, Cleveland

Editorial Comment

Historically, poisoning and the law meant one thing—murder. While that idea is not obsolete, its importance is severely curtailed, as Dr. Sunshine reveals in this article. Legal murder has been replaced by careless killing.

For the physician and attorney, several knotty problems arise within this paper. One wonders about the malpractice liability of a doctor who by telephone evaluates the potential salicylate poisoning of a child as a benign incident. The workmen's compensation and public liability aspects of a worker's being overwhelmed by carbon monoxide from a neighboring factory are daily medicolegal problems. But the most challenging thought to emerge from this study is the method of preventing the careless killing and injury surrounding modern society's use of poisons.

Control over poisons is paramount. Control by government at all levels—federal, state and local—is necessary. One example of federal control indicates how deeply into local affairs the United States government must extend for effective protection against dispensation of poison. Under the constitutional authority to "regulate commerce among the several states," Congress enacted the Federal Food and Drug Act. An integral part of the act requires proper labeling of dangerous drugs. In one case, sulfonamide tablets were produced in one state and shipped in a properly labeled bulk container to a wholesaler in a second state, who in turn sold to a retailer in the second state. The retailer removed the tablets from the lawful container and sold them to a consumer without the proper label. This apparently intrastate sale was the basis for a federal criminal conviction of the retailer for improper labeling. The dangerous drug was still considered to be in interstate commerce, for effective control on the consumer's behalf demanded the federal authority to extend to this depth in local affairs. United States v. Sullivan, 332 U.S. 633 (1948) is recognized as a historic precedent on the extent of federal authority.

At the same time, all control cannot be lodged in Washington, D. C. Local authority has a significant role to play. The past half decade has

(Continued on page A-64)

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witnessed the rapid growth of local community poison control centers to give not only emergency aid but also long-range education in the prevention of poisonings. Dr. Sunshine pioneered the Cleveland center. As chairman of the Education Committee of the American Association of Poison Control Centers, he seeks to expand knowledge and education for prevention. From today's medical experiences in these centers will come tomorrow's laws for prevention of poisoning, another example of medicine and law cooperating to serve society.—Oliver C. Schroeder, Jr.

IRVING SUNSHINE

CHEMISTS continue to make many new contributions which improve our everyday living conditions. Concomitant with these advances has been a rise in the number of chemical substances involved in poisoning incidents. Name the substance, and it is probable that it has been accidentally ingested at one time or another, sometimes with fatal consequences. Recent data reported by the United States Bureau of Vital Statistics indicated that in 1960 about 1500 deaths resulted from the accidental ingestion of chemical substances. These figures are minimal. Many sequelae to natural disease processes are similar to the symptoms one might expect from a poisoning incident. Conversely, poisoning symptoms may mimic those of natural disease. Unless a physician is suspicious, he seldom suspects that a chemical substance may have caused the observed symptoms and that a poisoning is involved. Consequently, if a fatality occurs, as in the situation just described, this death may not be reported as one due to poisoning.

Approximately 120 to 130 fatal poisonings occur in Cuyahoga County (Cleveland), Ohio each year. These represent about 10 per cent of the total number of violent deaths in this same area. Contrary to popular belief, homicidal poisonings (table 1) are infrequent occurrences. Most poisoning fatalities are accidental (58 per cent) or suicidal (41 per cent). The chemical agents responsible for these poisoning fatalities are also listed in table 1.

Toxic Agents

Carbon monoxide is responsible for more deaths than is any other chemical agent. This is true despite the fact that natural gas, containing no carbon monoxide, is used locally for heating and cooking. The purposeful or accidental exposure to the high concentration of carbon monoxide emanating from a gasoline engine's exhaust system causes many of these fatalities. Still other deaths occur in rooms where the oxygen supply is low because windows and doors have been sealed "to keep in the heat" and the gas appliance is faulty. This may result in incomplete combustion of the natural gas and, as a consequence, formation of the lethal carbon monoxide. In some of these situations the noxious gases cannot escape from the room because the heating appliance has a defective flue or, sometimes, no flue at all. Industry also contributes its share to the total number of carbon monoxide deaths. The unsuspected or accidental release of large concentrations of carbon monoxide formed or used in a particular industrial process has caused fatal accidents. The most novel case in our experience was that of a chimney worker who was working on a scaffold high above the ground. A sudden change in the wind direction was coupled with the accidental release of a large blast of carbon monoxide from a nearby stack. This gas surrounded the worker with a sufficiently high carbon monoxide concentration to make him dizzy, which caused him to topple to his death.

Medications cause more fatalities than do all other substances except carbon monoxide. Several factors contribute to this problem. The stresses of present-day living bring on physical and mental problems, some of which physicians try to relieve therapeutically. To assist them in this problem, the chemist has developed an ever-increasing number of valuable medications. Many patients' symptoms have been relieved with the prescribed use of these new drugs. Unfortunately, too many patients find permanent relief from all their problems

(Continued on page A-66)

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TABLE 1

FATAL POISONINGS* IN CUYAHOGA COUNTY, 1943 TO 1959, INCLUSIVE
SUBSTANCES INVOLVED AND MANNER OF DEATH

SUBSTANCES INVOLVED	NUMBER	MANNER OF DEATH	NUMBER
Carbon monoxide	804	Homicide	11
Sedatives	313	Suicide	638
Compounds of lead, arsenic or mercury	115	Home accidents	642
Corrosives, including cyanide	83	Industrial accidents	38
Alcohol (other than ethyl)	56	Accidents in other places	205
Salicylates	43		
Economic poisons	32		
Alkaloids	30		
Miscellaneous	58		
TOTAL	1,534	TOTAL	1,534

*Deaths due to ingestion of ethyl alcohol are not included.

by the indiscriminate use of these potent drugs. Some unstable people find specific suggestions for their own demise in news reports of the role of a particular drug in a suicidal death of a publicized person. In adults, barbituric acid derivatives are still the medications most frequently implicated in fatal poisonings. However, the recently developed sedatives and tranquilizers are beginning to contribute their share of fatalities as more and more people misuse them.

The salicylates also cause a significant number of fatalities each year, particularly in children. These valuable drugs bring welcome relief to headaches and to aching bones. They are found in everyone's medicine chest. Adults can and do use relatively large amounts of salicylates. Consequently, an adult is seldom perturbed when a youngster, who always tries to mimic his parents, takes a large dose of aspirin. However, the following sequence occurs frequently. "Doctor, what shall I do? Junior was playing with the headache medicine. Tablets are all over the floor. Powdered residues were on his clothes and around his mouth. He vomited and in the vomitus were parts of tablets. Right now, he's quiet and happy." Some physicians evaluate this situation as relatively benign and do not see the child or recommend any additional treatment, particularly since vomiting occurred. In some instances, the original call is followed by another, five or six hours later. "Doctor, Junior doesn't look good now; he's breathing very fast." "I'll meet you at the hospital promptly," is the response. At this stage, heroic therapy may or may not save the child. Parents should know that salicylate poisoning is a *serious* disease. Anyone who has ingested large amounts of salicylates must be seen by a physician. Only when he actually sees the patient can the doctor determine whether or not therapy is required.

Still high on the list of toxic agents, but fortunately decreasing in number each year, are the compounds of lead, arsenic or mercury and the solid inorganic acids and alkalies which are used as cleansers. Lead poisoning is peculiar to youngsters who live in overcrowded, poorly maintained homes where flaking paint prevails. These youngsters are chronically exposed to the old paints high in lead content. Many become ill; some become acutely ill. Twenty-five to 35 per cent of those who become acutely ill may die, and those who survive may have incurred permanent brain damage. Arsenicals and mercurials, as

(Continued on page A-68)

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TABLE 2

SPECIFIC AGENTS* INVOLVED IN NONFATAL POISONINGS IN CUYAHOGA COUNTY

AGENTS	HOSPITALIZED PATIENTS†				POISON CENTER CALLS‡	
	Number less than 18 years old		*Number more than 18 years old*			
Internal medications		1,072		278		1,959
Aspirin	662		62		683	
Cathartics	64				132	
Sedatives	45		144		129	
Cough medications	45		8		143	
Tranquilizers	24		20		69	
Anorectic agents	36		2		80	
External medications		138		83		516
Antiseptics	31		25		173	
Camphorated oil	14		8		44	
Liniment	14		6		47	
Household preparations		150		16		1,482
Paint	46				307	
Turpentine	40				111	
Cleaners		352		62		1,369
Bleach	124		22		212	
Caustic cleaners	66		11		106	
Disinfectants	25		9		46	
Furniture polish	32				133	
Soaps and detergents	39				379	
Cosmetics		53		10		867
Perfume	11				277	
Hair preparations	13				127	
Skin lotions	11				46	
Economic poisons		153		22		470
Rodenticides	73		16		54	
Insecticides	38		5		167	
Moth balls	30				107	
Solvents		61		5		186
Unknown		29		4		417
Miscellaneous						532
TOTAL		2,008		480		7,798

*Although totals are given for each major heading, only the most frequently involved substances are listed under each heading.

†These patients were admitted to the hospital over a one and one-half year period in 1958 and 1959. Data were not available from all hospitals for the entire period.

‡These cases occurred over a two and one-half year period in the years 1957, 1958 and 1959.

well as the corrosives, used to be the suicide's favorite tool. Slowly but surely potential suicides were educated that they need not suffer before they die. There are other and easier ways. "Reading all about it" in their daily paper is one way in which these potential suicides are educated.

Economic poisons are essential chemicals. Our exploding population could never be fed without the use of rodenticides, insecticides and herbicides. On all sides these valuable chemical agents are used effectively. However, they kill not only animals and weeds but also human beings. This is particularly true if one is unwise enough to handle these products carelessly or use them for purposes other than those for which they were originally intended.

(Continued on page A-70)

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TABLE 3

AGE OF VICTIMS OF NONFATAL POISONING IN CUYAHOGA COUNTY

AGE (YEARS)	HOSPITAL ADMISSIONS*	POISON CENTER CALLS†
Less than 1	54	352
1	463	1,685
2	707	2,206
3	424	1,012
4	157	348
5	52	147
6 to 9	40	182
10 to 18	111	571‡
More than 18	480	
Not given		1,295
TOTAL	2,488	7,798

*These hospital admissions occurred over a one and one-half year period in 1958 and 1959. Data were not available for all hospitals for the entire period.

†These calls occurred over a two and one-half year period in 1957, 1958 and 1959.

‡In these cases, the patients were more than 10 years old.

Another chemical substance that contributes directly or indirectly to a person's death is not included in the comprehensive list of poisons just discussed. Conspicuous by its absence is ethyl alcohol. Overindulgence in ethanol not only may be fatal but also may predispose ordinarily competent individuals to accidental death because of their loss of judgment and coordination while under its influence. In Cuyahoga County, ethyl alcohol was present in 60 per cent of the victims of homicide and in 50 per cent of the victims of fatal accidents. In connection with this problem, everyone can help save lives, maybe even his own. All he needs to do is practice moderation. If people who have been drinking must travel, they should be sure that the driver has not been drinking. This practice may save more lives than many vaccines!

Incidence of Accidental Poisoning

A fatality caused by a chemical agent is one consequence of accidental poisoning. Many people are poisoned but survive this insult. Present statistics indicate the ratio of nonfatal to fatal poisonings is high. Again, reliable statistics are difficult to obtain. In one large metropolitan area there has been a tenfold increase in the recorded number of cases of accidental poisoning. This probably is not due to a real increase but to better and more comprehensive reporting of the poisoning incidents that do occur. The incidence of nonfatal poisoning is also a real community problem. This type of accident occurs much more frequently than does fatal poisoning. In Cuyahoga County, approximately 4000 calls a year (10 to 12 a day) are now received at the local Academy of Medicine Poison Information Center (table 2). In addition to this, there are approximately 2500 reported cases at hospital emergency rooms and an unknown number of cases reported to and treated by local physicians.

Accidental poisonings occur most frequently in one to three year old children (table 3). These youngsters are naturally curious and explore their surroundings with all their developing senses. Foul smells, bad taste and hot or sharp objects do not frighten them until they learn or are taught that these are warnings they should heed if they want to survive to have other experiences. Parents seldom recognize that tranquilizers in the living room, reducing pills by the kitchen sink, anemia tablets in the purse, sedatives beside the bed, and headache pills in the medicine chest are potentially dangerous to their offspring. By law, the ever-present corrosives, ammonia, lye, toilet-bowl cleansers and iodine must carry poison labels to warn everyone of their lethal potential. To protect the users of economic poisons, legislation has been passed requiring proper labels on all containers of these products. Unfortunately, adults disregard these warning labels, and youngsters cannot read them. Most parents are unaware that many other common household products are also potentially dangerous. These products do not bear a warning label and usually are within easy reach of exploring youngsters.

A glance at table 2 indicates some of the products which cause trouble for children. These include bleaching agents, soaps and detergents, cosmetic preparations, painting supplies, drawing and writing materials, and furniture polishes, to mention only a few. How

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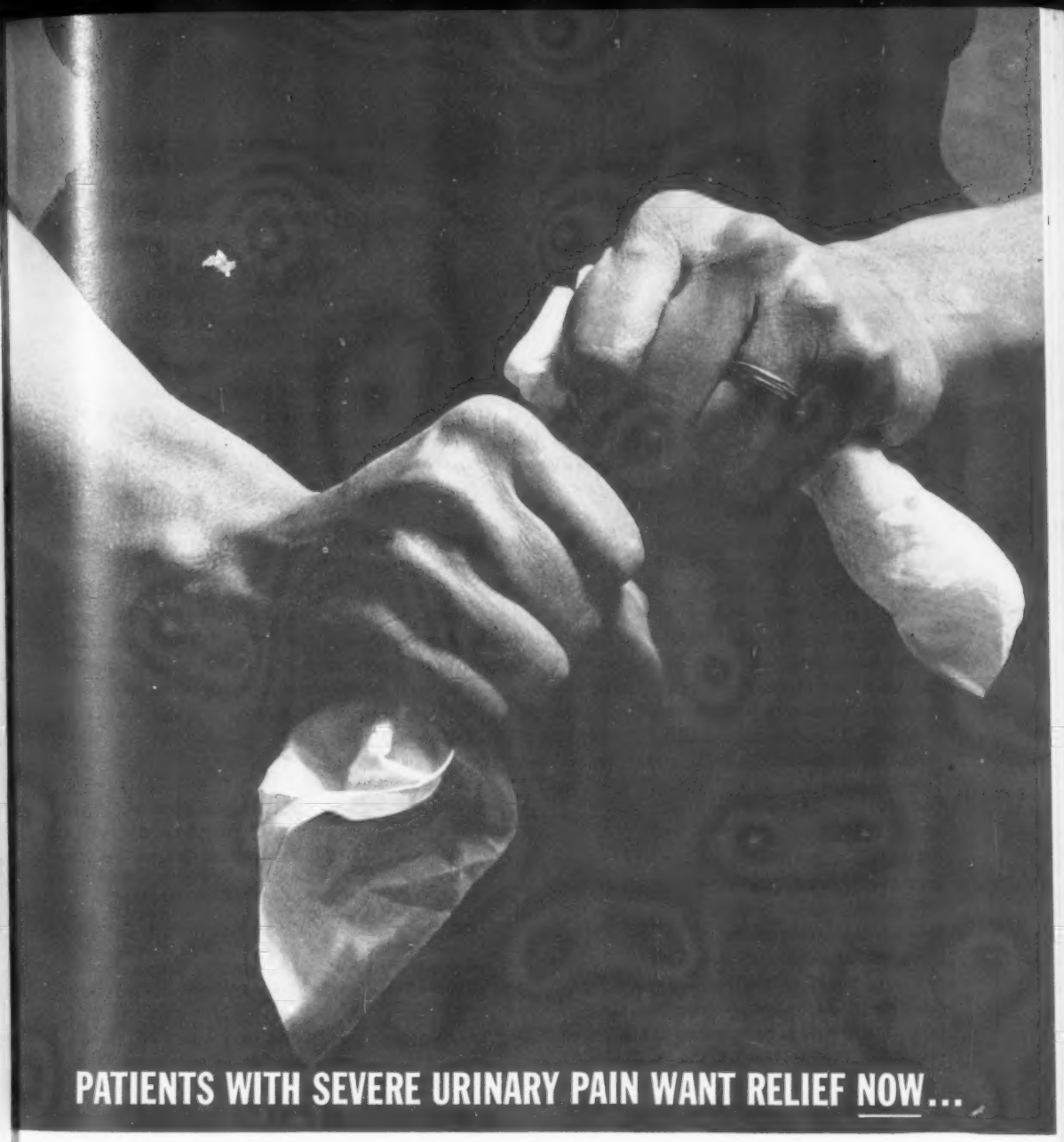

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do children get at the gallon jug of bleach? They do not have to. Mother usually measures one cupful for the wash. Just then the phone rings or Betty gets her fingers in the doorjamb, or any other distraction that plagues a mother's quiet day occurs. That is the very moment Junior decides he is thirsty, and here is a handy cup, full and ready. "Down the hatch" it goes, and in comes trouble. Daddy's storing kerosene and turpentine in soda pop bottles can result in the same thing. Why is furniture polish bad? The polish is not. The old cake wax was no problem, but the no-rub, no-work preparations which lighten mother's day contain solvents which cause a chemical pneumonitis if ingested, and children do drink these products when the colorful bottles are within reach. Next to a Christmas tree in appeal is milady's cosmetic assembly of shapely bottles with pleasing colors and alluring odors. Youngsters can no more resist these lures than can their fathers or the woman who uses them. Fortunately, most of these cosmetic products contain relatively little potentially harmful ingredients. Seldom therefore do untoward effects result from their ingestion.

Prevention of Accidental Poisoning

Faced with this rising tide of poisoning accidents, what can alert parents do? Experience has shown that the following practical suggestions for parents are helpful.

1. Protect young children and gradually educate them to the dangers involved. It is the same as teaching children safety when they cross streets or warning them not to play with fire.

2. Try to poisonproof the home. Out of reach and out of sight mean out of trouble.

3. Avoid storing small amounts of unused liquid household products in common drinking containers such as cups or empty soda pop bottles.

4. Do not coax sick children to take flavored medication by calling it candy. When the youngster gets better and decides he would like some candy, the results could be fatal. Children should be given medication only on the premise that it will help them get well.

5. Discard medications after a patient has recovered from a given illness. If medications are in use, do not store them at the youngster's eye level. Remember, prevention is the real key to the elimination of accidental poisoning.

Chemists can and do help in some poisoning emergencies. Those in industry are frequently called by personnel at poison information centers to help resolve the problem of the chemical composition of a household product and its potential toxicity. Other chemists are essential members of many poison information center staffs. Still others are called on to analyze biologic material obtained from a victim of accidental poisoning. These chemical analyses may help the physician to make an accurate diagnosis and prescribe proper treatment.

The clinical chemist and the toxicologist would welcome help in this particular area. As new products are developed and marketed, prompt publication of their physical properties and of analytic methods for their detection in tablets or from biologic media would be of inestimable value.

MEETINGS *and Postgraduate Courses*

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Radiology

PAUL C. HODGES*

Small Hiatus Hernia, Gastroesophageal Regurgitation and the Phrenic Ampulla

FREDERIC E. TEMPLETON†

University of Washington School of Medicine, Seattle

Dr. Frederic E. Templeton, who has practiced radiology in Seattle for 15 years, has special interest and proficiency in gastrointestinal radiology. Following graduation from the University of Washington and internship at the University of Wisconsin, he served as resident, instructor, assistant professor and associate professor of radiology at The University of Chicago from 1931 to 1943. During the Chicago period he studied in Germany and Sweden under a fellowship grant and began studies and professional friendships which have led to membership in the leading societies in this field, the authorship of a well-known book, and numerous journal articles.—Paul C. Hodges, M.D.

PATIENTS commonly complain of retrosternal discomfort associated with changes in posture. Avery Jones[1] quoted the imaginative patient as saying, "It's murder getting my shoes on. My stomach is in my chest, Doctor." At night, after much to eat and drink, he is wakened by a burning distress. His mouth fills with acid fluid regurgitated from the stomach. By drinking alkaline water or propping himself up on pillows, he eases the discomfort. The clinician often attributes these difficulties to hiatus hernia and, when the radiologist reports normal findings, calls attention to a small pouch above the diaphragm containing prominent folds, believing that a hiatus hernia was overlooked. When the radiologist insists that the structure is normal, the clinician wants to know if special maneuvers designed to demonstrate hiatus hernia were used in the radiologic examination. He has read about the use of a steep Trendelenburg position, a pillow under the patient's abdomen when he is prone, a tight band about the ab-

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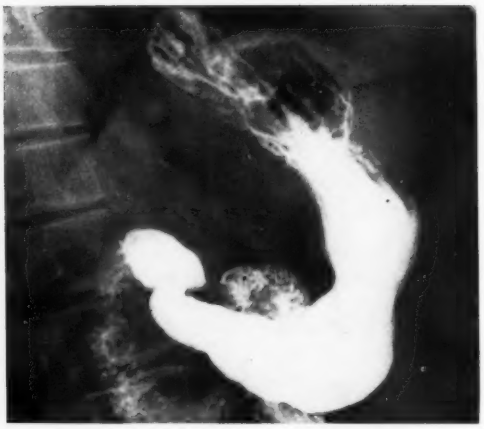

FIGURE 1. Extending upward from the stomach and bisected by the shadow of the diaphragm is a small pouch. Folds in the pouch are similar to those of the stomach. Absence of narrowing between pouch and stomach indicates that the esophageal hiatus is wide. Esophageal peristaltic waves cease at the apex of the pouch.

domen, an enema, and other means to increase intra-abdominal pressure. He knows of Evans and Bouslog's[2] report that hiatus hernia commonly occurs in pregnancy after the twenty-fifth week and disappears after delivery. The clinician is convinced that everyone who has heartburn and regurgitation has hiatus hernia (figure 1).

A restatement of the views held by different members of the profession concerning heartburn, regurgitation, small hiatus hernia and the small structure that frequently is seen radiologically at the lower end of the esophagus, considered by some to be a hernia and regarded by others as a normal structure, would seem to be worthwhile.

Two workers, one a radiologist and the other a surgeon, have expressed valuable opinions regarding the development of hiatus hernia which are stated and restated in different terms by different authors. The radiologist, Åkerlund,[3] in 1933, wrote:

> Under the manifold different causes . . . there begins a visceral protrusion up through the hiatus. The abdominal portion of the esophagus passes through first and then the adjacent portions of the stomach follow. This visceral protrusion in its very first stages assumes the character of a hernia without a hernia sack [*sic*] and only when the hernia has reached a certain size is there also a bulging of the peritoneum. The fact that there is in the beginning no peritoneal covering is according to the author no reason for naming the beginning visceral dislocation anything else than 'hiatus hernia,' or if one wishes, 'small sackless hiatus hernia.' . . . Thus the very beginning stages of acquired hiatus hernia are so common in this material that they can almost be called physiologic changes of age.

The surgeon, Harrington,[4] expressed a similar idea in 1940:

> The diaphragmatico-esophageal membrane and the loose attachment of the peritoneum at the cardia have considerable bearing on the occurrence of hiatus hernia. It is probable that the hiatus hernias of the elderly people which are accompanied by insufficiency of the hiatus are attributed to atrophy of this protective elastic membrane, particularly in cases in which there is an abnormally large hiatus. The elastic membrane has been sufficient during the prime of life to protect the opening but as the atrophy associated with the advancing years develops, the stomach is permitted to protrude through the hiatus to a position above the diaphragm. It is probable, in such cases, that this herniation would have occurred earlier in life had abnormal stress been applied, such as trauma, respiratory difficulty or marked increase in intra-abdominal pressure.

Åkerlund and Harrington postulate that weaknesses of the esophageal hiatus occur and allow a portion of the stomach to pass from the abdominal to the thoracic cavity. These weaknesses are associated with the atrophy of advancing years and are augmented by certain stresses and strains, such as trauma, respiratory difficulties, and increased intra-abdominal pressure.

In 1944, I[5] resurrected the term "phrenic ampulla" to designate a dilatation that normally occurs at the lower end of the esophagus and also described a ringlike sphincteric structure associated with the ampulla. Twelve years later, Schatski and Gary[6] described the structure in detail and suggested the term "lower esophageal ring." Both before and since these two publications, many pages in the literature have been devoted to criteria for differentiating

the normal phrenic ampulla from the abnormal hiatus hernia. The criteria usually have been derived from either surgical or postmortem observations. The surgeons rely on the size of the hiatus, stating that a normal hiatus accepts two fingers and an abnormal hiatus three or more. The size of the fingers is not stated. By the time the pathologist or anatomist dissects the region, rigor mortis is present. In most instances these gentlemen postulate physiologic states from fixed anatomic specimens. The widely quoted book by Lerche[7] is an example of this type of work.

Because a firm anatomic basis for differentiation of the ampulla from hernia has not been established, authors disagree on the numerical incidence of hiatus hernia. When special maneuvers are used to increase intra-abdominal pressure during the examinations, a higher incidence is reported.

Since the normal phrenic ampulla cannot be distinguished from a hiatus hernia by studying anatomic and pathologic material, it is logical to restudy the physiology of the lower portion of the esophagus. Avery Jones[1] expressed doubt that the structures demonstrated radiologically by means of special maneuvers which increase intra-abdominal pressure are hernias and that all the answers are known concerning the anatomy and physiology of the lower part of the esophagus. He questioned the presumption that all persons having regurgitation of acid gastric juice into the esophagus have hiatus hernia. In reference to sliding hernia, he asked, "What is the exact relation of competence of the cardia to hiatus hernia? Can it occur without hernia subsequently developing?" Referring to paraesophageal hernia, Jones stated that "as the esophagus enters obliquely into the stomach there is no free regurgitation back into it." That regurgitation does not occur in paraesophageal hernia is explained not only by the angle at which the esophagus enters the stomach but also by the buffer of a large herniated pouch.

Also important to recall is Brick's[8] opinion that hiatus hernia, regardless of size, may be asymptomatic, is often demonstrated accidentally, and can be accompanied by other lesions responsible for the symptoms. For these reasons, it is difficult to determine from the literature how frequently hiatus hernia occurs without symptoms.

Johnstone,[9] a radiologist, pointed out that his clinical colleagues expect the radiologist to produce evidence of a hiatus hernia whenever other investigations exclude such lesions as coronary thrombosis, cholecystitis and gastric ulcer. The difficulties are lightened, in his opinion, if the radiologist studies the physiologic rather than the anatomic aspects of hiatus hernia. At radiologic examination he found that the intradiaphragmatic portion of the esophagus is nonexistent and that the stomach and esophagus fuse at the hiatus. He did not confirm the hypothesis that the mucosa moves upward during belching. When clips were placed on the mucosa and the diaphragm moved downward, the clips remained stationary, giving the illusion that they moved upward. In one illustration, Johnstone demonstrated that clips placed at the level of the esophagogastric mucosal junction lie above the diaphragm.

Johnstone also said that having the patient bend over has no advantage over routine methods of examination in producing evidence of hernia or regurgitation. He found it impossible to demonstrate a hernia if the patient's diaphragm is not relaxed as in belching.

Most contemporary physiologists agree that the lower end of the esophagus appears and acts differently from the rest of the esophagus. Code and co-workers[10] found a barrier of increased pressure interposed between the esophagus and the stomach, about 1.5 cm. in length during inspiration and about 2 cm. during expiration. They called it the high-pressure zone. Bettarello's group[11] reported that in some patients the zone measures approximately 5 cm. in length.

Hill and associates[12] and Tuttle and his group,[13] working with electrodes and meters for determining the pH in the lower part of the esophagus and the stomach, confirmed the statement made by Jones and others that acid gastric juice of low pH regurgitating into the esophagus can cause distress in the lower thoracic and upper abdominal regions. Whether or not the regurgitation of gastric juice of

FIGURE 2.

a. The lower esophagus, distended by barium forced toward the stomach by a peristaltic wave, shows a bilateral indentation, the lower esophageal ring.

b. The wave has almost reached the contracting ring.

c. The wave does not continue beyond the ring. The segment beyond the ring remains distended. The diaphragmatic hiatus remains distended.

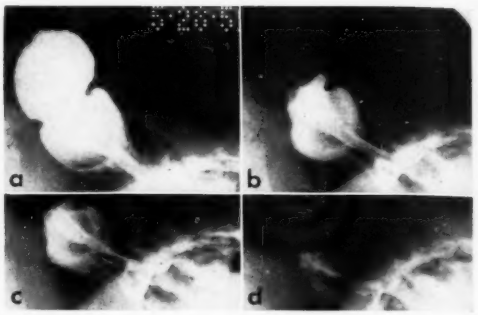

FIGURE 3.

a. The lower esophagus is ballooned out. The peristaltic wave has not reached the lower esophageal ring. The dilated lower esophagus appears to be divided into two pouches by the ring.

b. The peristaltic wave has almost reached the ring. The ring has contracted only slightly, and the segment on the left is more prominent, producing the illusion of a notch.

c. The wave has reached the notch. The lumen seen at the ring in (a) is smaller, and the segment below is still dilated.

d. The segment below the ring is contracted. Fluoroscopic observations, confirmed by films made with a fast-changing apparatus, indicate that the lower dilated segment contracts simultaneously in a manner similar to the contraction of the duodenal bulb.

low pH always produces symptoms is not established. Not all the patients studied by these two groups had hiatus hernia. In those who did, Hill and associates, like Brick, found that "often these symptoms coexist with other gastro-intestinal abnormalities. It is nearly impossible to decide whether the hiatal hernia is responsible for the complaints and should be operated upon." I have examined some patients in whom surgical intervention did harm, probably because improper diagnosis was followed by procedures that disrupted the normal physiologic function of the normal lower esophagus and diaphragmatic hiatus.

Radiologic Demonstration of Esophageal Contractions

The different contractions that the lower esophageal segment undergoes are easily confirmed at radiologic examination. Esophageal peristalsis slows and eventually ceases in most patients about 2 to 5 cm. above the diaphragm at or close to the lower esophageal ring or notch (figure 2; figure 3a, b and c). The segment between the diaphragm and the point at which peristalsis ceases may not contract, and a bulbous dilatation may persist. This dilatation is often called a hiatus hernia. Or the segment may contract completely, leaving a narrowed channel (figure 3d). When this occurs, some observers using cinematography conclude that the lower segment responds to esophageal peristalsis; but surely the cinematographic changes recorded by the physiologists do not support this conclusion. Their findings indicate that the structure is not a hernia. It is related to Code's zone of high pressure and the phrenic ampulla, a structure amplified by increasing the resistance against which esophageal peristalsis works. Increased resistance is produced by contracting the diaphragm with the Valsalva test, swallowing "uphill" in the Trendelenburg position, and increasing intra-abdominal pressure. The reader will recognize that these procedures are recommended to demonstrate "hernia" in patients with gastroesophageal regurgitation.

That the region of the phrenic ampulla responds differently from the rest of the esophagus is also evident in some pathologic conditions. In achalasia, the dilated section of esophagus usually lies several centimeters above the diaphragm (figure 4). The portion between the dilated section and the diaphragm is contracted. Strictures and peptic ulcers usually occur several centimeters above the diaphragm at the site of the ring or notch, not at the diaphragm (figure 5). The portion

FIGURE 4. In a patient with cardiospasm (achalasia), the lower 4 cm. of the esophagus is tightly contracted.

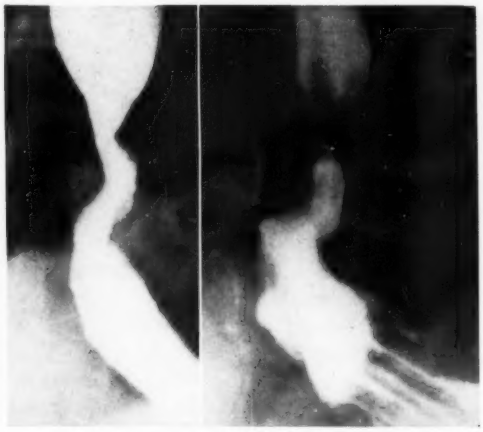

FIGURE 5. An elongated ulcer that narrows the lumen of the esophagus lies about 5 cm. above the diaphragm. The diaphragmatic hiatus is broad. Peristalsis progresses as far as the ulcer. The fact that esophageal peristalsis progresses to within 5 cm. of the diaphragm indicates that the segment below the ulcer is ampulla and not stomach drawn into the thorax by cicatricial contraction.

between the stricture or ulcer and the diaphragm is contracted. Carcinomas immediately above the diaphragm usually are adenomatous, not squamous, the type that occurs in the esophagus above the esophageal ring.

Clinically, the problem is not so much the anatomic appearance of the lower segment of the esophagus as it is the mechanics. In a person whose mucosa is susceptible to the action of acid gastric juice, regurgitation may cause esophagitis, ulcer and stricture. If the mucosa is not susceptible to acid or if the juice is not acid, nothing abnormal happens. The obese patient whose intra-abdominal pressure is raised by excessive mesenteric fat is more likely to have trouble than the slender patient. It is established that increased intra-abdominal pressure plays a part in producing gastroesophageal regurgitation and perhaps hernia in some patients, but it is not known why similar processes do not occur in all patients. Some workers postulate a "guard mechanism," such as an oblique insertion of the esophagus into the stomach, a pinchcock action of the diaphragm, pressure of surrounding organs causing an abrupt kink of the subdiaphragmatic portion of the esophagus, an intrinsic esophageal sphincter, or puckered mucosa which prevents the retrograde flow of aliment by closing the cardiac orifice.

Conclusion

New thinking and reinterpretation of old evidence indicate that the structure lying at the lower end of the esophagus, called either the phrenic ampulla or a small "sliding" hiatus hernia when extra effort is exerted to bring out the dilatation, differs physiologically and responds differently to pathologic influences from the rest of the esophagus. This structure is more closely related to the stomach physiologically than to the esophagus and appears as a part of the stomach anatomically when the hiatus is large. For these reasons, it may be a part of the stomach located normally above the diaphragm. Much work will be required to establish its exact nature. One thing is sure: Patients who experience gastrointestinal regurgitation and heartburn do not all have hiatus hernia.

It is proved that acid gastric juice and not an abnormally dilated lower esophageal segment produces heartburn and probably other symptoms commonly attributed to hernia. Here is a reason why neither the surgeon nor the radiologist, both of whom can determine accurately the width of the hiatus, can help

the clinician to determine the cause of the patient's symptoms. Neither can tell if a wide hiatus allows gastric contents to flow into the esophagus, even though experience indicates that heartburn is more frequent in patients in whom the hiatus is wide.

Perhaps as the surgeon and radiologist learn more of the physiology of the lower part of the esophagus and of the processes that control the diaphragm about the hiatus they will differentiate accurately the small hiatus hernia from the phrenic ampulla and explain the causes of gastroesophageal regurgitation. Paying more attention to the types of esophageal contractions will certainly help the radiologist. At present, methods designed to estimate the pH of the lower esophageal segment are the best ways of finding out why a patient says, "It's murder getting my shoes on. My stomach is in my chest, Doctor."

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IN BRIEF

ATARAXOID contains the glucocorticoid prednisolone and the ataractic agent, hydroxyzine.

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ADMINISTRATION AND DOSAGE: ATARAXOID dosage varies with individual response. Clinical experience suggests the following daily dosage: *Initial therapy*—4-6 **ATARAXOID** *5.0* Tablets. *Maintenance*—1-4 **ATARAXOID** *5.0* Tablets or 2-8 **ATARAXOID** *2.5* Tablets. After initial suppressive therapy, gradual reduction of prednisolone dosage should begin and continue until the smallest effective dose is reached. Prescribe in divided doses, after meals and at bedtime.

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PRECAUTIONS AND CONTRAINDICATIONS: Usual corticosteroid precautions should be observed. Incidence of peptic ulcer may increase on long-term prednisolone therapy. However, therapy has often been maintained for long periods without adverse effects. Contraindicated in infectious disease including active tuberculosis (except under close supervision), peptic ulcer, certain infections of the cornea, such as dendritic keratitis, superficial punctate keratitis, epidemic keratoconjunctivitis, and in patients with emotional instability. Caution is indicated in the treatment of diabetic patients and patients with severe cardiovascular disease, and in some cases sodium restriction and potassium supplementation must be considered.

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*Warter, P. J.: Prednisolone-hydroxyzine combination in rheumatoid arthritis, J. M. Soc. New Jersey 54:7, 1957.

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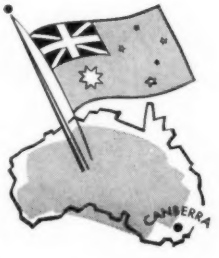


Acute "cholestatic syndrome"—In the *Medical Journal of Australia*, Drs. R. A. Joske, L. R. Finlay-Jones and E. G. Saint, University of Western Australia, Perth, have discussed a number of conditions in which pseudo-obstructive jaundice occurs without any recognizable cause. The authors prefer the nonspecific term "cholestatic syndrome" to describe these disorders.

A diagnosis of acute cholestasis was made in 15 patients who had jaundice with negative results of flocculation tests and no mechanical obstruction of the biliary tract. The outstanding clinical observation was the variance in manifestations of the disease in men and women. In general, men with the condition were older than were the women affected. In men, itching and weight loss were relatively more frequent and jaundice was of greater degree and longer duration. In women, there was a positive relation between pregnancy and the disorder.

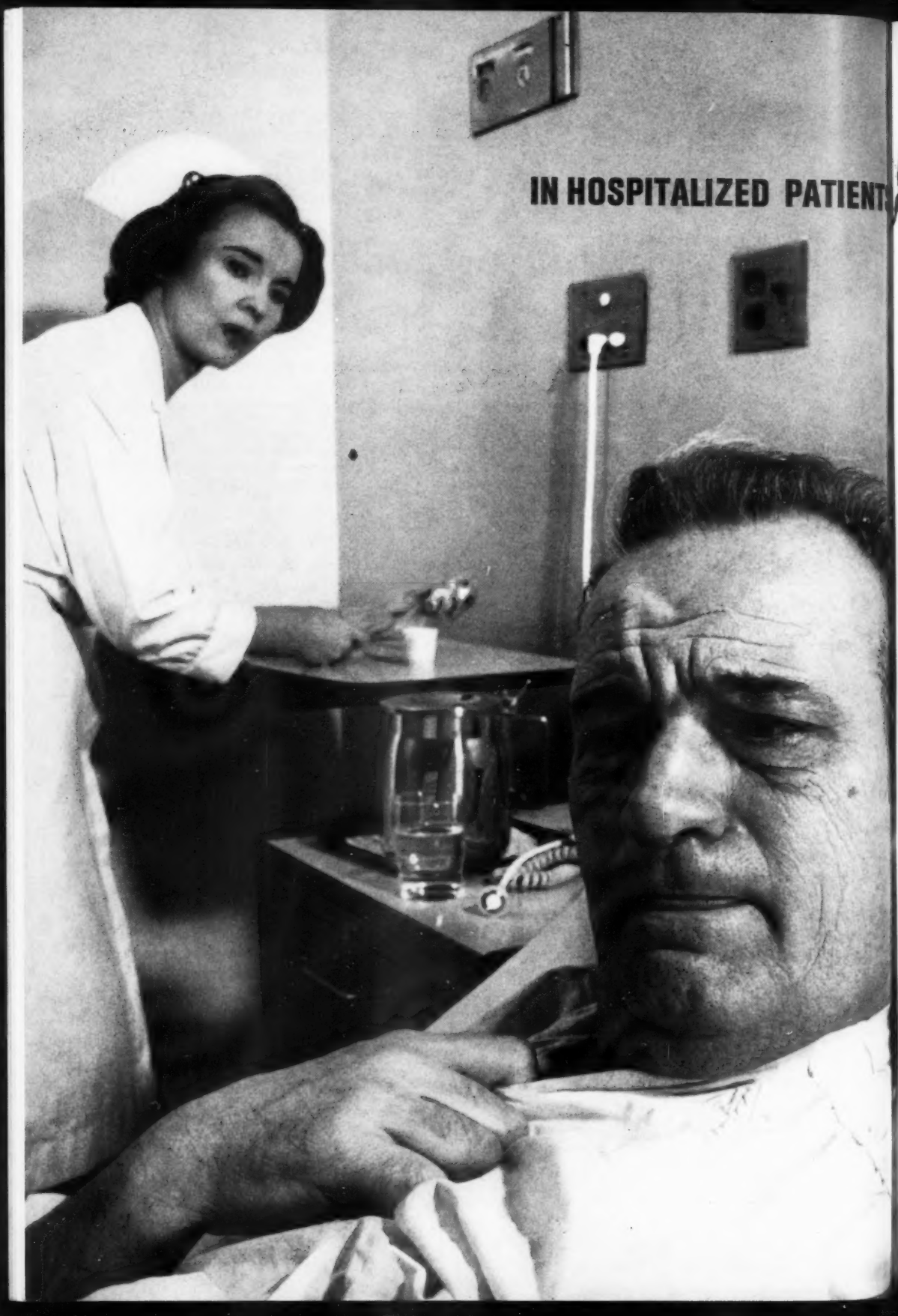
In both sexes, the onset of the disease resembled that of viral hepatitis. Initial examination revealed jaundice and weight loss. None of the patients evidenced the stigmas common to chronic liver disease, nor was the gallbladder palpable in any of them. Elevation of the serum alkaline phosphatase level occurred in 12 of the 15 patients.

Histologically, certain features of aspiration biopsies performed in all patients were more or less constant. In the portal tracts there was a mild to moderate increase of fibroblasts, polymorphonuclear leukocytes and lymphocytes, without appreciable bile ductule proliferation. The parenchymal cells showed patchy necrosis and evidence of bile retention in the form of bile thrombi and intracytoplasmic granules; the latter was usually more marked in the central lobular areas. Fibroblastic activity occurring under the stimulus of acute liver injury rarely progresses to the formation of mature collagen, and this was not seen in biopsies obtained three months after the onset of jaundice.

Operative findings were similar in 10 of the 15 patients who had laparotomies. The liver was enlarged, firm on palpation, and green in color. The capsule had a finely nodular appearance. The gallbladder and bile ducts were collapsed; when opened, they contained "white bile." In all patients, the external biliary tree was explored and found normal; this finding was confirmed by cholangiography. All patients withstood the operation well.

A study of more recent cases has shown that

(Continued on page A-90)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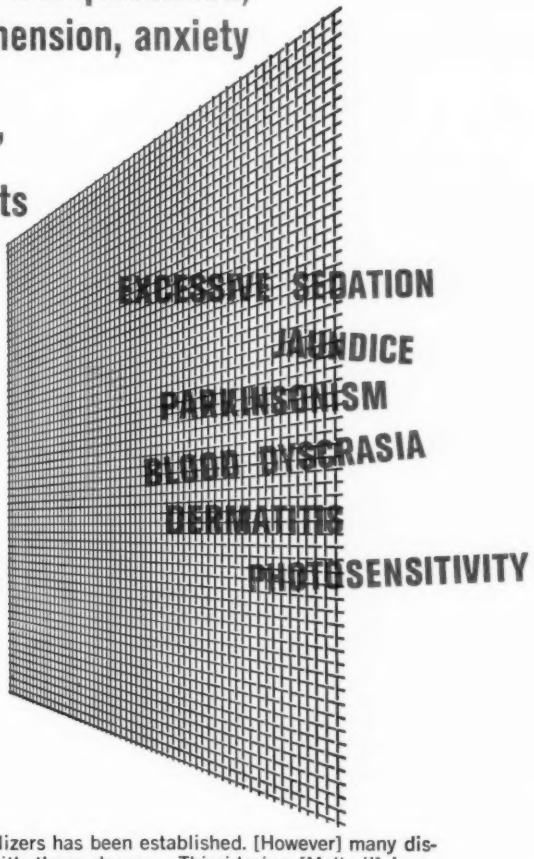

"The value of the phenothiazines as tranquilizers has been established. [However] many distressing side effects have been reported with these drugs.... Thioridazine [Mellaril] is as effective as the best available phenothiazine, but with appreciably less toxic effects than those demonstrated with other phenothiazines."[1]

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ORIGINAL RESEARCH SERVING THE PHYSICIAN

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correctly interpreted biochemical investigations are of value in diagnosing the acute cholestatic syndrome. Characteristic findings include a moderate to large increase in the serum bilirubin level, with negative flocculation but without much elevation of the serum alkaline phosphatase level. When these findings are associated with an increased serum glutamic oxaloacetic transaminase level, diagnosis may be made on biochemical grounds.

BRAZIL

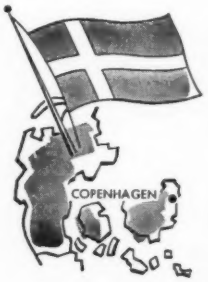
Manson's schistosomiasis—The increasing number of cases of Manson's schistosomiasis in the state of São Paulo has been discussed by P. Jabour in *Arquivos dos Hospitals da Santa Casa de São Paulo.* This increase is the result of a large migration of carriers of Manson's schistosomiasis from northeastern Brazil, where the disease is endemic and where more than three million cases have been reported.

Arantes noted the first cases of Manson's schistosomiasis in Santos in 1923; since these were reported, many others have been observed in the same city. In 1952, Amaral and Pires reported the first case in the hinterland of São Paulo. Later studies have indicated that the Paraíba Valley is the principal center of the disease.

Jabour discussed the case of a 41 year old man who was born in the Paraíba Valley and who worked in the stagnant water of the rice fields. The classic itch developed after the patient bathed in this water. When first seen, the patient had paraplegia, with sphincter disturbances and hypesthesia of the lower part of the abdomen and the lower limbs. He had no fever. His liver was slightly enlarged 2 cm. below the costal margin. His spleen was percussible, but not palpable. The results of the urinalysis and the Wassermann test were negative. The blood count showed 18 per cent eosinophilia; the serum protein was normal. Myelographic studies, liver function tests, and the Queckenstedt-Stookey test showed no abnormalities. Examination of the spinal fluid showed 16 cells per cubic millimeter. Ova of *Schistosoma mansoni* were found in the stool, and a rectal biopsy revealed both living and dead ova. A biopsy of the liver showed granuloma with ova of *S. mansoni.*

Following treatment with glucantime (*N*-methylglucamine antimonate), examination of the stool yielded negative findings and rectal biopsy showed only a few dead ova. The patient's neurologic condition improved progressively, but this could not be related directly to the specific treatment. Since myelography did not reveal an intraspinal block, surgery was not performed.

DENMARK



Aminophylline in treatment of cerebral infarction—The value of aminophylline in treating cerebral infarcts has been discussed in *Ugeskrift for laeger* by Dr. Bent de Fine Olivarius. This agent apparently promotes cardiac output and thus increases cerebral blood flow, especially in and around the anoxic cerebral lesion.

Twenty-nine patients who had cerebral encephalomalacia of recent onset were treated with one or more intravenous injections of 200 mg. aminophylline. The drug was administered to over one-half of these patients within 48 hours after the apoplectic seizure. In 22 patients, varying degrees of improvement of the neurologic deficit were immediately observed; the effect was permanent in 13 patients and temporary in nine. In the remaining seven (all of whom were hemiplegics), no improvement was noted. Slight improvement tended to be temporary, while a more pronounced effect usually was permanent. In one patient who previously had had jacksonian seizures, a focal epileptic seizure was provoked by the injection; no other side effects were observed.

If no reaction to aminophylline occurred, the prognosis for remission of the neurologic manifestations was poor. When an improvement (even though temporary) was noted, the eventual degree of remission was either more marked or the same as that seen immediately after the injection. Definite improvement after administration of aminophylline suggests the presence of

(Continued on page A-92)

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functioning collateral vessels and may indicate the use of anticoagulant therapy.

In vitro sensitivity of Neisseria gonorrhoeae to antibiotics—In *Ugeskrift for laeger*, Dr. Alice Reyn has reported on the results of tests for the sensitivity of gonococcal strains to penicillin, streptomycin, tetracycline and sulfathiazole. Testing was done by a tablet method from 1958 through February 1960 and by a plate dilution method thereafter. With the latter method, results were expressed as the 50 per cent inhibitory concentration and recorded in micrograms per milliliter.

In 583 strains isolated from January 1958 through February 1960 and tested for sensitivity to penicillin (sensitivity strains) by the tablet method, the sensitivity distribution was similar to that in strains tested in 1957, with a tendency toward a higher proportion of less-sensitive strains. Results of tests done by the plate dilution method on 265 strains isolated from February 1960 to August 1960 also showed the same range of variance as that noted in 1957. Comparison of the sensitivity strains with 102 strains sent in for diagnosis (diagnostic strains) revealed a much lower proportion of resistant diagnostic strains, thus confirming the statistically significant difference between these strains that was observed in 1957.

The same strains which were tested with penicillin also were tested with streptomycin. With the tablet method, a sudden increase of resistant strains was noted in January and February 1960. With the plate dilution method, a much higher percentage of resistance was found among sensitivity strains than among diagnostic strains.

With tetracycline, the plate dilution method was used to test 208 sensitivity and 102 diagnostic strains. Both groups fell within the range established in the 1957 tests. Findings in tests performed on 351 additional strains from October to December 1960 revealed a tendency toward a higher percentage of resistant strains. With sulfathiazole, 265 sensitivity strains were tested with the plate dilution method. A comparable percentage of resistance among sensitivity and diagnostic strains was observed.

Positive and statistically significant correlations were found among the inhibitory concentrations of all four antibiotics. It also is noteworthy that 68 sensitivity strains required more than 2000 μg. streptomycin per milliliter and at least 0.15 μg. penicillin per milliliter for complete inhibition.

ENGLAND

Advances in x-ray television—During the past five years there have been considerable advances in England in the use of x-ray television in medicine. The relative advantages of the various types of apparatus depend on the clinical information required. For the urologist in particular, the ability to watch the movements of the pelvis and ureter has opened up a new vista of clinical investigation, and one cannot now contemplate retrograde pyelography without visual control. However, not all types of apparatus available are of equal value to the urologist, whatever the radiologists may think; there are certain basic requirements. First, viewing of the screen or monitor must be binocular, and two or more persons must be able to view it simultaneously. It is not sufficient for the urologist to be told what the radiologist sees; he must be able to see for himself. Secondly, this viewing must be possible without acrobatics. The original monocular eyepiece was unsatisfactory in both respects. In nontechnical language, a bright visual image can be produced easily on any standard fluorescent screen by the use of a high x-ray output. Unfortunately, such x-ray dosage can be utilized for very short periods only, and this has always been the limiting factor in fluoroscopy.

The development of television for fluoroscopy has proceeded on two distinct lines. In the older systems, an image-intensifier tube provides the light gain, and a vidicon camera is then used to scan the output phosphor, thereby producing a visual image on an orthodox television monitor. The most recent development in this field utilizes a completely different principle. The necessary light gain in this system is obtained by the use of a very sensitive orthicon television camera, which scans a modified conventional fluoroscopic screen, the final visual image being produced on a special high-definition, 1,024 line television monitor. Provided a minimal light signal is received by the orthicon camera, the brightness and contrast of the monitor can be controlled entirely by manual adjustment.

In the *British Medical Journal*, Mr. Howard G. Hanley, surgeon, and Drs. F. G. Greenwood and M. Gilbert Scott, radiologists, Hillingdon Hos-

(Continued on page A-94)

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pital, have discussed recent advances in x-ray television with special reference to urology. Retrograde pyelography, they point out, has been completely revolutionized by the use of visual screening under an intensifier, and this examination is now seldom performed without visual control. The advantages are many: Not only can the dynamics of filling and emptying be studied visually, but the value and quality of the spot films are improved, while special areas of the tract can be accurately localized. The ureteral catheter can be passed in the operating theater or on the x-ray table, and it takes only seconds to visualize the tip of the catheter on the screen and to fill the pelvis under direct vision. The dangers of overfilling and the frustration of underfilling are eliminated, and a small spot film is taken at the optimal moment.

The equipment also is very useful for examining the pharynx and esophagus when conditions are ideal, with high contrast between the air-filled lung and the barium. In orthopedics an enormous field is available which surgeons have not yet had the time to cover. Fluoroscopy during hysterosalpingography is now performed routinely, and the use of magnification technic opens up a new field of research in the effect of relaxant drugs on the fallopian tubes. In no other investigation is the reduction of radiation dosage so important.

ISRAEL

Potassium perchlorate in thyrotoxicosis—In the scientific supplement of *Harokeach Haivri,* Dr. Z. Levitus has discussed the pharmacology and the clinical use of potassium perchlorate. At Beilinson Hospital, Petah Tiqva, experiments with radioisotopes showed that potassium perchlorate is not metabolized in mammals and that it passes unchanged into the urine. However, it is concentrated in the thyroid gland in a manner similar to iodine. Since it competes with iodine in the trapping mechanism of the thyroid gland, it reduces the amount of iodine in the gland; thus, less thyroxin is formed.

In clinical trials, Dr. Levitus found that potassium perchlorate was effective in approximately one-third of 35 patients with thyrotoxicosis. It cannot be recommended as a general substitute for the usual antithyroid drugs such as propylthiouracil. However, it is useful in patients who have allergic or toxic reactions to other drugs, since it is nontoxic and causes only minor side effects. Potassium perchlorate may also be worth a trial in patients in whom exophthalmos is developing rapidly as a result of treatment with thiouracil. It has seemed to be especially effective in some cases of juvenile thyrotoxicosis.

The first effects of treatment are seen six to eight weeks after the start of therapy. An increase in weight is one of the first signs; the reduction in the pulse rate and in the basal metabolic rate occurs later. Dr. Levitus warned that iodine should not be given during or soon after a course of potassium perchlorate, since it may cause severe exacerbation of the thyrotoxic symptoms.

Imipramine and cardiovascular complications—A. Atsmon and J. Pinkhas, of Beilinson Hospital, Petah Tiqva, have reported in *Harefuah* that cardiovascular complications occurred in three patients receiving imipramine, a drug used increasingly in treating depression.

The first patient was admitted to the hospital with a myocardial infarction after taking imipramine for two months. Administration of imipramine was continued in the hospital; however, 18 days later, severe precordial pain recurred, and the drug was discontinued. The patient recovered without further complications. The second patient, who had had a myocardial infarction four months previously, was started on imipramine because of depression. Three weeks after this treatment was begun, he was admitted to hospital with severe precordial pain. The electrocardiogram showed transient changes only, and there were no clinical signs of myocardial infarction. The third patient, a woman aged 52, had been taking imipramine for four months when she was admitted to hospital with severe precordial pain. The electrocardiogram showed only minor changes, but eight days later she died suddenly. At autopsy, only slight atheroma of the coronary arteries was found, with no evidence of myocardial infarction.

Although there is no proof of a causal connection between the use of imipramine and the occurrence of cardiovascular complications, the authors believe it wise to limit the use of this drug in disease of the coronary arteries.

Steroids in Infection

RALPH TOMPSETT*

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Steroids should prove beneficial in the management of patients with severe infections. However, their use is still poorly defined and further study is needed as to their administration and effects.

The effects of steroids in treatment of various infectious diseases are described and their limitations and hazards discussed.

In general, it is emphasized that when steroids are used, the duration of therapy should be restricted and, whenever possible, suitable antimicrobial drugs should be administered at the same time.

RALPH TOMPSETT

As soon as cortisone and adrenocorticotropic hormones became available, observations were made on their effects in patients with a variety of infections. Administration of these drugs in virtually any infection was found to bring about a profound change in the patient, with defervescence and marked symptomatic relief. This dramatic series of events is now in the realm of experience of almost every physician. So dramatic are these effects that after such an observation, even in only one seriously ill patient, one can scarcely avoid concluding that here indeed must be an exceedingly useful therapeutic tool. Even knowing the hazards, which by now have been well documented, the conviction is likely to persist.

Today, after a number of years of experience with the use of steroids in a wide variety of infections, the same questions must still be asked as were asked in the beginning. Are steroids ever of value in the management of an infection? Are there means of utilizing the seemingly beneficial effects of steroids without exposing the patient to excessive hazards? Certain more fundamental questions must also be brought up. Are the basic mechanisms of action of steroids or the basic mechanisms of infection well enough understood to permit the use of steroids in infections under certain well-defined conditions? Unfortunately, at the present time there are no precise answers to these important questions.

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TABLE 1

ACTIONS OF CORTICOSTEROIDS IN INFECTIONS IN MAN AND EXPERIMENTAL ANIMALS

1. General depression of host resistance
   - Effects on inflammatory response
   - Effects on reticuloendothelial system
   - Effects on antibody production
2. Activation of latent infections
3. Defervescence
4. Detoxifying effects
5. Reversal of hypersensitivity reactions
6. Replacement therapy of adrenal insufficiency
7. Potentiation of pharmacologic action of therapeutic agents
8. Increased exposure of infectious microorganisms to antimicrobial drugs

It is the purpose of this paper to review some of the laboratory and clinical observations on the use of steroids in infections in an attempt to assess the present status of their utilization.*

In table 1 are listed a number of effects of steroids which appear to be related to the over-all effect of these drugs in infections. In man and in experimental animals the administration of corticosteroids causes a general depression of host resistance to infections. Certain aspects of this effect appear to be in part understood. Corticosteroids reduce the inflammatory response to the invading microorganisms. They have certain effects on the reticuloendothelial system, and they affect antibody production.

Steroids may activate infections which under normal circumstances would be expected to remain latent. Perhaps equally important is the fact that the administration of steroids may give rise to infections by microorganisms which under virtually all other circumstances are saprophytic. Defervescence in the febrile patient is the rule. Detoxifying effects of steroids have been thoroughly documented. Reversal of hypersensitivity reactions, normally a part of certain infections, may be effected. Replacement therapy in the presence of adrenal insufficiency is clearly the most logical place for the use of steroids. The action of certain pharmacologic agents may be potentiated by the use of steroids. Finally, there is a possibility that the steroids may provide increased exposure of the infectious microorganisms to antimicrobial drugs.

It will be noted that in listing these effects, no attempt has been made to separate the harmful effects from the potentially beneficial ones. Although it is always tempting to try this, in only the most general way can it be done and with only a few of the actions of the steroids in infections.

At the outset, it may be said that in general the effects of administration of corticosteroids in the presence of infection are usually manifested in such a way that one must conclude that resistance to infection has been depressed. The extent of this effect varies conspicuously with the dosage, the type of steroid given, the particular animal species, the duration of administration, and the nature of the infection itself.[1,2] A wide variety of specific infections have been treated with steroids, and in virtually every instance the patients have shown prompt defervescence and loss of toxicity.[1-3] In the bacterial infections, which are those most readily studied, evidence frequently has been obtained that spread of the infection occurs under the effects of steroids or at least that increased multiplication of the microorganisms occurs. This has been observed in pneumococcal and mycobacterial infections, brucellosis and a variety of other conditions. In viral infections this has also been observed to some extent, but it is perhaps not so well characterized as in bacterial infections. In infectious hepatitis, for example, the apparent initial beneficial effects may be followed by an unexpectedly high incidence of relapse. In infectious mononucleosis or in mumps orchitis, however, relapse after the use of steroids has not been a frequent problem. In other instances, such as trichinosis, the immediate beneficial effects appear to have been well maintained. In some infections, such as poliomyelitis and acute streptococcal infections, it has been reported simply that no apparent harm has been done by the administration of steroids.

*Because of the limitations in the bibliography here the reader is referred to references 1, 2 and 3 which provide detailed bibliographies.

Mumps orchitis has been considered to be a special instance. Rapid subsidence of symptoms has been observed, and generally this subsidence has been considered to be more rapid than could possibly have been expected in the normal course of the disease. Nevertheless, testicular atrophy and azoospermia have occurred even after the use of steroids. Recently it has been questioned whether any beneficial effect accrued. Indeed, even the symptomatic effects have been questioned, and in a well-controlled study a group treated with a placebo appeared to be relieved of symptoms as promptly as those patients treated with steroids.[4] Despite some variation in these observations, there is little question that rapid subsidence of the inflammatory response may occur.

The effects of steroids in activating malaria and tuberculosis, among other infections, naturally have turned attention to the activity of macrophages and reticuloendothelial cells under the influence of these hormones. In experimental animals infected with tubercle bacilli, large numbers of extracellular bacilli are noted in lesions under the influence of steroids. The recent work of Benacerraf and his associates[5] has suggested a mechanism of this effect of steroids. Their studies have shown that cortisone does not affect the uptake of particulate matter by the reticuloendothelial system of mice. Once the reticuloendothelial system has been maximally loaded, however, cortisone significantly delays its recovery to the preloading stage in which it is again able to take up injected test doses of particulate matter. These experiments afford one explanation for the accumulation of large numbers of unphagocytized bacteria in tissues under the influence of steroids.

The effect of steroids on the production of antibodies remains a complex question. The results observed vary markedly with the dose of antigen, the initial state of the host, the time of administration, the dose of the hormone, and other factors. In general, relatively large doses of steroids are required to bring about a significant depression of antibody formation, and the effects of steroids on antibody production under most circumstances would seem to have little effect on the outcome of an infection.

Ample evidence attests to the fact that new infections may develop under the administration of steroids. A variety of types of pneumonia, septicemias, endocarditis, active pulmonary tuberculosis, deep mycoses and some unusual saprophytic infections have been observed.[1,2] It has been repeatedly observed that the administration of large doses of steroids to experimental animals permits the emergence of fatal infections due to many different microorganisms, often such normally saprophytic species as *Corynebacterium*. The gravity of this sequence of events in man is attested to by the 12 fatal cases of varicella which have been reported in children receiving steroids. It is particularly troublesome to note that the symptoms and the usual signs of infection in these patients are often masked. It is worthy of note here in considering the over-all problem of steroid effect in infection that in the natural history of Cushing's disease infection is the leading cause of death.

Enhancement of infection and reactivation of latent infections have been demonstrated in many animal studies. Infections which normally heal spontaneously or which are normally mild or chronic in animals may be converted into rapidly fatal infections just by administration of steroids. It may be recalled here also that steroids are used to assist in the demonstration of infectious agents. For example, in the manufacture of poliomyelitis vaccine this has proved to be of value.

There is little question that steroids may bring about a prompt reversal of many hypersensitivity reactions. In the case of infectious diseases it remains difficult to separate the influence of that part of the inflammatory response which is due to hypersensitivity. It would seem that hypersensitivity in tuberculosis may be of considerable importance; yet the value of steroids in reducing this has not been clarified. In such circumstances as varicella pneumonia where a considerable element of hypersensitivity may be present, steroid effect has sometimes appeared favorable despite the inherent dangers noted in its use in varicella itself.

In theory the most obvious advantage of the use of steroids in infections would be as replacement for adrenal insufficiency per se. The experiments of Kass and Finland[6] on the effects of cortisone on pneumococcal infections in mice have demonstrated very nicely the relationship of adrenal function to recovery from infection. They have shown (1) that adrenalectomy increases susceptibility to infection, (2) that optimal steroid therapy in adrenalectomized animals restores them to their original state of resistance to infection, and (3) that animals receiving less or more than optimal steroid therapy have a reduced resistance to infection. These studies demonstrated well that adequate replacement therapy will return animals to essentially the same state as the intact animal with respect to infection but that excessive doses again depress resistance. Similar conclusions have been reached on the treatment of tuberculosis in patients with Addison's disease.

The question remains as to whether adrenal insufficiency actually exists in most cases of infection. Kass and Finland,[6] in discussing this, pointed out that there is reason to suspect that adrenal insufficiency is relatively rare in severe sepsis. They noted that hemorrhage and degenerative changes can be produced in the adrenal gland by stimulating it with corticotropin and not only as consequences of exhaustion, hypoxia and sepsis. They noted also that there is evidence that vascular collapse occurring in severe sepsis is usually not due to adrenal insufficiency. They pointed out that the circulating hydroxycorticosteroid levels in patients in collapse due to sepsis, when measured in their laboratory, have almost always been in the high normal or elevated ranges and that similar levels have been found in cases of infections without collapse. They stated that levels of hydroxycorticosteroids comparable to those found in patients with Addison's disease have not been noted in patients with severe sepsis.[7]

In clinical practice, the most convincing example of the possible occurrence of adrenal insufficiency in infections is in meningococcemia with the Waterhouse-Friderichsen syndrome. The administration of steroids is generally recommended in this situation. Nevertheless, the evidence to date is not impressive that steroids make a significant change in the outcome in this disorder. The largest series thus far reported is that of Tobin[8] in which five out of nine such patients survived. This is perhaps no better than might be expected under normal circumstances with the utilization of norepinephrine and without steroid therapy.

One may rightfully raise the question as to whether small doses of steroids might be significantly better than the doses usually employed. Indeed, this has been suggested and certain observations have been made that relatively small doses may increase resistance to infection in normal as well as adrenalectomized animals. It is significant that the range of dosage employed in these animal experiments is a narrow one. Slight increases above the optimal amount resulted in again decreasing resistance to infection. Although this question is intriguing, one may only be permitted to speculate on it at the present time, since the evidence that adrenal insufficiency occurs in severe infections remains uncertain.

Perhaps related to the question just discussed is the possible role of steroids in potentiating the action of either epinephrine or norepinephrine. Such an action would be expected to be beneficial to the individual in peripheral vascular collapse. The significance of this observation is not clear, however, since there is also experimental evidence that in certain types of vascular collapse the response to epinephrine or norepinephrine may be augmented without the administration of exogenous steroids.

The hormones may, of course, show a profound effect in reducing "toxicity" using that term in the usual clinical sense. In general terms, this may readily be demonstrated in patients with infection. Experimentally, it is well shown in the response of animals to pyrogens. Protection against bacterial endotoxins from a variety of sources has been shown. There is considerable variation, however, within species and with different animal species. This evidence has been reviewed in detail by Kass and Finland[6] and will not be reviewed

again here. Suffice it to say that although steroids can protect animals against a wide variety of toxic agents, this is not an entirely nonspecific effect in that certain toxins can be shown to be uninfluenced by the steroid effects. The antipyrogenic effect may conceivably be an effect on the hypothalamus and, indeed, hypothermia may be a problem in patients with infection to whom steroids are given.

A minor effect of steroids has been considered to be the possibility that reduction of the inflammatory response and the predominance of extracellular microorganisms associated with diminished phagocytosis may result in an increased exposure of the infectious agent to antimicrobial drugs simultaneously administered. Certainly the extracellular location of certain bacteria, notably tubercle bacilli, under the administration of steroids is well known. The same circumstance, however, would appear to result in vastly increased numbers of microorganisms within tissues. In general, studies in animals would suggest that in infections in which adequate coverage by antimicrobial drugs can be assured, short-term therapy with steroids does not produce a major hazard as far as the existing infection is concerned.

Specific Application of Steroids

So much for the general principles which are involved in the administration of steroids to patients with infections. We may now review a few of the infections in which there has been the most interest and in which the experience with the administration of steroids is greatest. Certainly the most common situation in which steroids are now employed occurs in patients with a variety of infections who experience peripheral vascular collapse. It seems impossible at the present time to decide whether an ultimately beneficial effect may be obtained in such patients. Controlled studies on this subject are being carried out at the present time and may provide definitive answers to this problem. It seems clear, however, that when steroids are used, it is most advisable to employ them for only short periods.

Among the bacterial infections which may be discussed are pneumococcal meningitis, meningococcal infections, typhoid fever, brucellosis and tuberculosis. A report of very favorable results in the management of pneumococcal meningitis has been made by Ribble and Braude[9] who reported 11 survivals in 12 patients treated with both steroids and penicillin. If additional experience in a larger series confirms these results, this would represent an important addition to the management of this serious infection.

Use of steroids in meningococcal infections with shock has already been reviewed. Suffice it to point out here that the supposed benefits of the administration of steroids in the Waterhouse-Friderichsen syndrome should not obscure the need for the use of pressor agents, such as norepinephrine, which have seemed to be clearly of benefit.

In typhoid fever, steroids may have beneficial effects when administered together with chloramphenicol. It has been clearly demonstrated that this can be done safely in patients who are seriously ill, but in the vast majority of patients it would appear that steroids are unnecessary. The same may be said of brucellosis. Here again, in seriously ill patients steroids may be administered safely and they may be lifesaving. Nevertheless, the number of patients with brucellosis for whom steroids are required must be very small.

The use of steroids in peripheral vascular collapse and Gram-negative rod septicemia has already been mentioned. Suffice it to say that although at present the administration of steroids in this situation is common practice, it is far from clear that it improves the therapeutic results.

In tuberculosis at least three situations may arise in which steroids have proved to be of value: (1) In patients gravely ill with either meningeal or pulmonary disease caused by drug-susceptible tubercle bacilli, steroids may "buy time" to achieve the benefit of antimicrobial therapy. (2) In Addison's disease due to tuberculosis of the adrenals, replacement therapy is clearly indicated. (3) In patients who exhibit hypersensitivity reactions to the antituberculous drugs, steroids may permit the continued administration of the drugs.

Steroids have been said to be helpful in the management of tetanus. Here there appears to be a sound basis for their use in experimental animal studies. Nevertheless, the experience to date would suggest that certainly steroids constitute a minor, if indeed even a beneficial, part of the management of tetanus.

The use of steroids in viral and rickettsial infections may be mentioned briefly. It should be recalled that in none of the viral infections are there specific antimicrobial agents available with which to prevent spread of the infection. This gives one considerable pause in ever administering these hormones. The experience to date would suggest that in infectious mononucleosis prompt relief of the more severe manifestations of the disease, such as the central nervous system complications, can be brought about without ultimate damage to the patient. Again, it is advisable that therapy be given only for a short time. Mumps orchitis has already been discussed. In this disease, too, steroid therapy certainly should not be routine, if indeed it is ever indicated.

The use of steroids in infectious hepatitis has been reviewed by Nelson.[10] Here steroids appear to be of benefit in the more acutely ill patients with infectious hepatitis. Again, it is an unusual situation in which it appears necessary to use the drugs, but this is certainly an area in which further exploration of the beneficial effects of steroids should be done.

Favorable reports on the use of steroids in encephalitis due to measles have been made, although others have felt that no beneficial effect was obtained in this disease. In the remainder of the viral infections the use of steroids has been so limited and in general the infections so mild that information is not available on which to base an opinion of drug effects. It would appear that seldom, if ever, are these hormones indicated in the rickettsial infections.

The same may be said of the use of steroids in the mycotic diseases. The common practice of using steroids to reduce toxicity of amphotericin in the treatment of histoplasmosis has led to a belief that the steroids are probably not harmful when administered in this way. Evaluation of this disease is difficult, however, and such an opinion should be regarded with caution. Certainly in Addison's disease occurring as a complication of histoplasmosis, steroids are clearly indicated.

It has already been mentioned that malaria may be activated by the administration of steroids. Nevertheless, beneficial effects have been reported and seem quite striking in the management of blackwater fever, a rare complication of malaria.[11] In trichinosis, also, there may be a definite value in the administration of steroids in the more severe cases.[3]

In conclusion, I would like to refer to the study of Lepper and Spies[12] who reviewed their experience with steroid therapy in a large number of patients. This was not planned as a systematic study but did review three periods in their hospital. In the first period of two years only small amounts of steroids were used in a few patients. In the second phase a wave of enthusiasm led to the administration of large amounts of steroids over a two year period. Finally, for the last three years, their use was limited to bacterial meningitis. These investigators concluded: "The use of adrenal or adrenotropic hormones did not contribute to the successful treatment of such patients (with acute infections) when used as indicated by clinical judgment."

Summary

This report has reviewed some of the evidence concerning the use of steroids in infections both from the standpoint of the fundamental knowledge of their action and from the clinical experience to date. The major conclusion one can make is that the immediately observed beneficial effects in many patients with infections still suggest that steroids should prove to be of considerable value in the management of severe infections. The exact indications, mode and duration of administration, and other factors are poorly defined and point up the need for much further study in this area. It is recognized that in only a few circumstances has it been well established that steroids are not harmful and in even fewer that they are clearly beneficial in the final analysis. It is clear, however, that in most situations, administration of steroids is at-

tended with a considerable risk of aggravating the existing infection, as well as a risk of activating latent infections or permitting new infections to arise.

Finally, it should be stressed that when steroids are employed in the presence of infection, every effort should be made to restrict the duration of therapy and, whenever possible, to administer suitable antimicrobial drugs at the same time.

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Use and Abuse of X-ray Therapy for Benign Skin Conditions

WITH PARTICULAR REFERENCE TO X-RAY ATROPHY

DONALD M. PILLSBURY*

University of Pennsylvania School of Medicine, Philadelphia

DONALD M. PILLSBURY

It is the author's opinion that 500 r is the maximal safe total dose of ionizing radiation (half-value layer of 1.0 to 2.0 mm. of aluminum) in fractional doses at weekly intervals that should be given to the skin in treatment of a benign dermatosis; moreover, soft irradiation (grenz rays) will produce as good results in many dermatoses as standard superficial x-rays, with less risk of late sequelae. If a sharp and persistent erythema is produced by any single exposure, x-ray atrophy is almost certain to follow, even though it may be delayed for years. X-ray atrophy of the skin following treatment of a benign dermatosis is the most completely preventable of all serious human diseases.

THE title of this paper was suggested by the scientific program committee for this Assembly. I accepted it without any change, but a certain degree of imbalance became clear during preparation of the discussion, with a much greater emphasis on *abuse* than on *use* of ionizing radiation for the treatment of benign dermatoses.

In four previous publications, the most recent in 1956, several colleagues and I have discussed x-ray therapy of skin diseases from various standpoints, always with a plea for conservative, cautious, competent use of this modality. The reactions from auditors and readers have been vigorous and surprisingly divergent. The subject continues to be a topic for lively discussion and controversy between extremists in both conservative and liberal camps. What I shall say will displease some readers. There is far from unanimous agreement among therapists as to which diseases

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Presented before the forty-fifth annual Assembly of the Interstate Postgraduate Medical Association at Pittsburgh.

of the skin are amenable to x-ray therapy, the allowable limits of gonadal exposure, the higher incidence of leukemia following exposure, and the risks of atrophic changes and cancer of the skin. This discussion will deal principally with aspects of the problem with which I am personally familiar, namely, the effectiveness of such therapy in various skin diseases and its potentialities in the production of skin cancer.

More than a decade ago, Crumay and I[1] wrote: "The continued advances in the knowledge of etiologic factors in skin diseases make re-evaluation of accepted methods of treatment necessary.

"It is particularly advisable that such repeated evaluation be made in the case of methods of treatment capable of producing harm, especially irreversible harm. There can be no question that roentgen therapy of skin diseases, regardless of the possible potentialities for good, is a . . . method of treatment which, if used unnecessarily or inexpertly, is capable of producing two of the most irreversible of all skin lesions, x-ray atrophy and skin cancer. Any active consultant in the fields of radiology, surgery, or dermatology has . . . encountered many patients in whom late sequelae of roentgen therapy for benign skin conditions have occurred and in whom the disease thus produced far surpassed the skin lesion originally treated, in terms of morbidity and mortality."

In recent years I have, with some confidence, anticipated seeing very few *new* cases of x-ray atrophy in my own clinical experience. The reasons for this confidence (now downgraded to uncertain hope) are as follows. The calibration of superficial therapy units reached a high degree of accuracy by 1930; the list of diseases in which x-ray therapy is indicated has been greatly restricted by effective antibacterial and anti-inflammatory compounds; general physicians, dermatologists and radiologists are receiving better training in the principles and technics of radiotherapy; an attitude of distinct conservatism in respect to x-ray therapy has become increasingly evident among specialty groups chiefly responsible for such therapy; facts and propaganda regarding the harmful potentialities of radioactive isotopes and ionizing radiation have been widely disseminated in the lay and technical press. That the total number of cases of cancer of the skin due to ionizing radiation has been greatly decreased I have no doubt, though accurate figures are not available. It is also true that most new cases of x-ray-induced cancer of the skin are seen in patients who received their initial treatments more than 10 or 20 years ago. Nevertheless, new instances of such malignancy continue to appear in my experience, and in many of them the last x-ray treatment was administered a very few years or even months ago.

Much has been written regarding the genetic effects of ionizing radiation. These effects are striking and undoubted in insects and plants. Man's liability to such mutation remains to be determined, but there seems little doubt that there are significant risks and that scrupulous precautions against unnecessary gonadal irradiation must be taken in all radiologic diagnosis and therapy.[2]

The leukemia-producing potentialities of ionizing radiation are much more clear-cut and impressive, although many dispute the interpretation of available data in relation to ordinary diagnostic and therapeutic use of x-rays. Dameshek and Gunz[3] concluded that "of the various etiologic factors proposed for leukemia in human-beings, the only one that appears to be rather conclusively established is that of ionizing radiation. The evidence for this includes (a) the incidence of leukemia in radiologists, which is 8 to 10 times as great as that in physicians in other fields; (b) the incidence of leukemia in those surviving the atomic blasts near the hypocenters of Hiroshima and Nagasaki, which is 12 times as great as that in survivors at the periphery of the blasted areas; (c) the relatively high incidence of leukemia in individuals in Britain and Holland treated for spondylitis by x-rays; (d) the development of leukemia in individuals treated for enlarged thymus by x-rays; and (e) possible leukemogenic effects on the baby of the taking of a roentgenogram of a pregnant woman's abdomen to determine fetal size and position. In addition, there are nu-

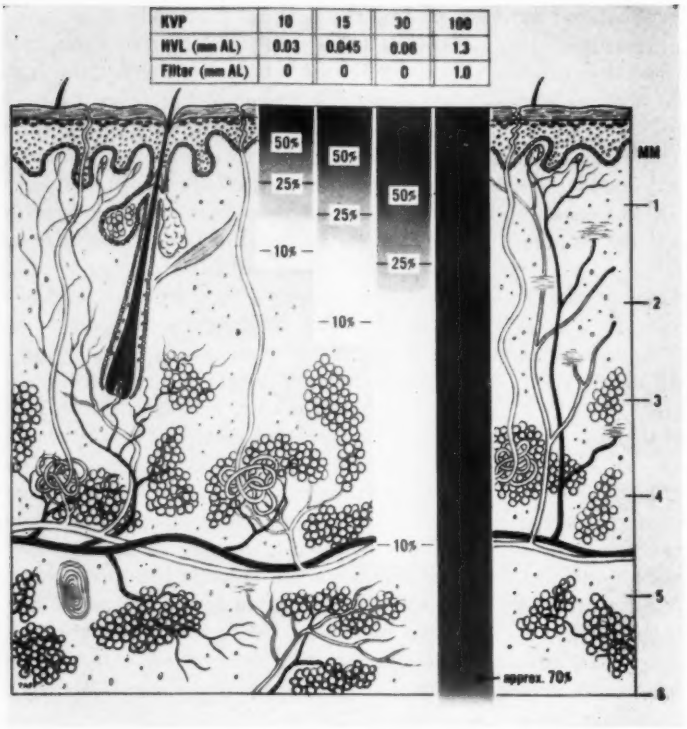

FIGURE 1. Schematic scale representation of penetration of x-rays of varying wavelengths into skin. KVP indicates the peak kilovoltage at which the rays are generated. HVL represents the half-value layer of aluminum, the thickness which will reduce by one-half the x-rays passing through it.

From Pillsbury, Blank and Madden.[4]

merous experiments in animals including those showing the leukemogenic effects of x-rays and nuclear irradiation."

As to the relation of ionizing radiation to late atrophic effects on the skin and to an increased incidence of skin cancer, there cannot be the slightest doubt. Such cases are commonplace. The principal area of inadequate information on this problem concerns the question of the level of irradiation to the skin that may be regarded as completely safe, whether given in a single large dose or in divided doses over months or years. A major factor in the production of x-ray atrophy is the careless and routine use of such treatment.

Various factors play a role in the production of late atrophy from x-rays. The effects of sunlight are additive to those of x-rays, and an amount of irradiation tolerated well on a covered portion of the body will produce unquestionable late effects on exposed portions. This becomes a matter of great practical importance in the treatment of conditions such as chronic dermatitis involving the hands and forearms or acne. The gross and microscopic changes seen in exposed areas of skin in aged persons often are indistinguishable from those produced by ionizing radiation.

A second important factor is the passage of time. A rather large dose of x-rays is less likely to produce significant late effects in the skin of a 70 year old person than in the skin of a 20 year old person. I have observed a great many persons in whom the atrophic effects of x-rays did not become evident grossly until 20 years after the last exposure. Indeed, such changes may not become really overt and troublesome until 30 or 40 years later.

Physical Factors Relating to X-ray Therapy in Dermatologic Disease

It is not within the scope of this paper to outline in detail the wide range in quality of the x-ray therapy available. Figure 1 illus-

trates the types of radiation in common use in dermatologic therapy at present. Through the use of thin beryllium window tubes, very soft, long-wave x-rays generated at low kilovoltage may be administered.[4] X-rays produced at lower kilovoltages have a short penetration into the skin. However, a few rays will penetrate below the level at which all but 10 per cent have been filtered out by the tissues. The trend in dermatologic x-ray therapy is toward lower kilovoltages, from 10 kv (the so-called grenz range) up to 30 or 40 kv. With such rays, the effects of the ionizing irradiation are more largely restricted to the diseased areas of the skin and there is less risk of damage to underlying blood vessels, ancillary glands and connective tissue. Regardless of the quality of the irradiation used, it is possible to produce late x-ray atrophic effects, but with rays in the very low kilovolt ranges a much larger cumulative dose is allowable.

One rule holds for all types of radiation, regardless of quality: *If a sharp and persistent erythema is produced by any single exposure, x-ray atrophy is almost certain to follow, even though it may be delayed for many years.*

Maximal Tolerated Dose of X-rays

The amount of roentgen irradiation that can be given to the skin in a single dose without producing immediate sequelae is reasonably well known, but there is considerable difference of opinion as to the total amount that may be administered without risk of late atrophic sequelae, which may occur two, three of four decades later.

Perusal of standard textbooks on radiologic and dermatologic therapy reveals wide variations, expressed or implied, in the amount of x-radiation that may be administered safely to large areas of skin in the treatment of benign dermatoses. While all writers warn against overexposure (and are thus solidly allied against sin), only a handful of statements as to the dividing line between safety and danger are available. Loosely stated directions for x-ray treatment of various benign dermatoses can in many instances easily be interpreted as justification for exposing the skin to total amounts of well over 2000 r. In a recent paper on dermatologic x-ray therapy, Cipollaro[5] stated that in treatment of acne vulgaris his routine procedure for the past 20 years has been to give 75 r of low-voltage unfiltered x-rays, having a half-value layer of between 0.5 and 0.75 mm. of aluminum to each side of the face, once weekly to a maximum of 16 treatments "over a period of 24 weeks." If more therapy is necessary, it may be given after a year, and eight further treatments are allowable. This is a total of 1800 r given to each side of the face. Cipollaro stated further that patients who have received 2400 r show no deleterious effects after 20 years. I have personally questioned many therapists throughout the country, both dermatologists and radiologists, and have never found one who believes that a total dose of 1800 to 2400 r given to the face is anything but excessive.

The only extensive follow-up survey that has been made of patients who have received fractional superficial x-ray therapy is that of Sulzberger, Baer and Birota,[6] who compared the skin of 1000 dermatologic patients who had been treated with low-voltage roentgen rays 5 to 23 years previously with the skin of 1000 patients who had not been given x-ray therapy. Approximately 165 patients who had received more than 1000 r showed evidence of "mild roentgen sequelae." The writers concluded that "as long as the total of not more than 1000 r is given in fractional doses, roentgen rays, as used by most dermatologists in this country, are safe or safer than other accepted forms of therapy." However, this conclusion is open to considerable question on the basis of the data presented.

Andrews[7] stated, "In most cases it is inadvisable to give the sum total dose of over 800 r" (in the treatment of acne).

It is my opinion, shared by a considerable number of radiologists and dermatologists with whom I have discussed the problem, that 500 r is the maximal truly safe total dose of ionizing radiation (with a half-value layer of 1.0 to 2.0 mm. of aluminum) which should be given to the skin in the treatment of a benign dermatosis. Some therapists will regard this opinion as ultraconservative. I am,

FIGURE 2. Severe late x-ray atrophy after treatment of acne. Note beaked nose, blotchy pigmentation and telangiectasia. Because of repeated epitheliomas, many of the "submarine" type which could not be detected early, extensive excision and plastic repair were advised. The patient committed suicide before these procedures could be carried out.

moreover, convinced that very soft irradiation in the so-called grenz range will produce fully as good results in many superficial inflammatory dermatoses as will "standard" superficial

FIGURE 3. Atrophy of skin and underlying structures of palm following prolonged x-ray therapy for chronic eczematous condition of unknown etiology. Treatments had been given over a period of 15 years, in spite of the fact that no single treatment or course of treatment seemed to have any beneficial effect. The last treatment had been given on March 7, 1960, two weeks before this photograph was taken.

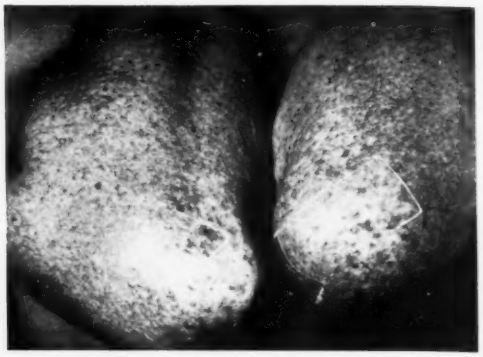

FIGURE 4. Radiodermatitis of elbows following x-ray therapy for psoriasis. Because of repeated painful ulcers, excision and plastic repair were undertaken—a very tedious and difficult procedure.

x-rays and with far less risk of undesirable late sequelae.

Figures 2 through 7 illustrate examples of late x-ray atrophy following the treatment of various dermatoses. In most of these cases, unfortunately, an accurate record of the total amount of irradiation or its exact quality is not available. However, there is sufficient evidence to indicate that the total cumulative dose was of an order considerably in excess of 1000 r, and probably well over 2000 r.

Some Salient Facts Related to X-ray Atrophy and Cancer of the Skin

Several salient facts stand out relating to x-ray atrophy and cancer of the skin caused by ionizing radiation. Many are so obvious as to hardly deserve mention, and I list them only because they are often ignored.

1. X-ray atrophy of the skin following the treatment of benign dermatoses is the most completely preventable of all serious human diseases. It is predominantly iatrogenic but to some extent "quackogenic."

2. X-ray atrophy of the skin represents an irretrievable acceleration toward tissue death. The progress may be slowed by various precautions but it is never reversed.

3. Skin atrophied by x-ray is highly vulnerable. Its defensive capacity against all types of physical and chemical assault is severely reduced.

FIGURE 5. X-ray atrophy following treatment of large hemangioma in a child. Such therapy is rarely necessary in strawberry-type hemangiomas, because spontaneous involution is the rule, and it should never be of an order which will produce late atrophic effects or damage to underlying epiphyses.

4. The incidence of cancer in skin atrophied by x-ray is inordinate. The relation between physical damage and neoplasm is clear and unquestionable.

5. The progression of x-ray atrophy is hastened by two prime additive factors, sunlight and the passage of time.

6. The psychic trauma of x-ray atrophy of the skin is profound. On exposed areas the appearance of the skin may be so changed and grotesque as to interfere seriously with the patient's occupational and social survival. Even more traumatic is the threat of malignant change, an almost inevitable sequela if the patient lives long enough.

7. Surgical procedures involving skin atrophied by x-rays are poorly tolerated. The decreased vitality of tissue and the restricted blood supply regularly result in delayed healing, whether from curettage of a small superficial keratosis, an ordinary excision biopsy,

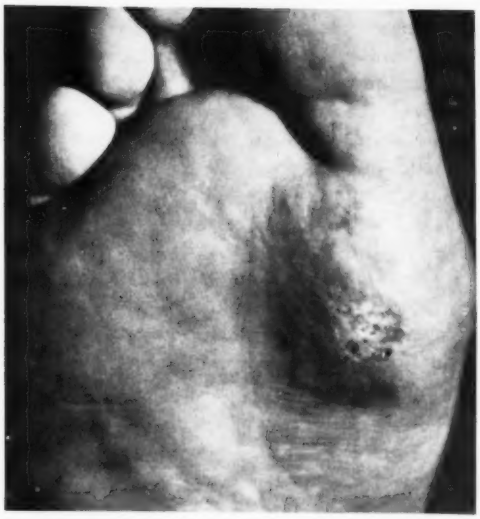

FIGURE 6. Severe atrophy and ulceration following single x-ray treatment for plantar warts. The area did not tolerate any weight bearing. Plastic repair was eventually fairly successful.

Figures 2, 3 and 6 are reproduced from "Manual of Cutaneous Medicine," by D. M. Pillsbury, W. B. Shelley and A. M. Kligman (Philadelphia, W. B. Saunders Company, 1961).

or more extensive excision and plastic repair. I agree entirely with Royster and Lehr[8] that surgical repair of x-ray atrophy of the skin for purely cosmetic reasons is unjustifiable except for the occasional small lesion that can

FIGURE 7. Severe atrophy and ulceration following x-ray therapy for "bladder papillomas" administered by a medical quack.

be excised completely and closed primarily. In extensive x-ray atrophy the decision regarding surgical intervention must be dictated by the threat of malignancy and must be made with the full realization that the cosmetic result will never be really good, that failure and disappointment will plague the most expert surgical management at times, that a satisfactory result will be achieved only in about 25 per cent of cases, and that death from metastatic malignancy may not be preventable. These statements are, I trust, sufficient comment on the tragedy of x-ray atrophy following the treatment of a nonmalignant dermatosis.

Preventive and Therapeutic Measures

Once atrophy of the skin has occurred following the use of ionizing irradiation, certain preventive and therapeutic measures may be helpful.

1. The patient and physician should recognize that the affected areas of the skin are vulnerable. Sunlight is especially harmful, and overexposure is to be avoided scrupulously and effective sun-screen creams are to be applied as needed. Chemical irritants and exposure to biting cold and to wind may be poorly tolerated.

2. Regular inspection is advisable; intervals of six months are not too frequent. A magnifying loop is essential to an adequate examination.

3. Keratotic or otherwise suspicious-looking small lesions should be removed promptly, *always with biopsy*. Obviously *superficial* lesions may be removed easily by curettage under local anesthesia, with electrocoagulation of the base.

4. Scarred and thickened areas should be evaluated with the greatest care. A small miliary tumor may be the "periscope" of a "submarine" tumor which has surfaced only with difficulty through the scarred and thickened area.

5. Consultation and joint discussion with a dermatologist and a plastic surgeon are advisable in every case of extensive x-ray atrophy.

6. Gentle understanding and supportive psychotherapy are essential ingredients of management, even of the apparently stoic patient.

Possible Indications for X-ray Therapy in Nonmalignant Dermatoses

Acne—X-ray therapy is not recommended for acne. It has never been established, by means of a controlled study wherein one side of the face was treated by irradiation, that x-ray therapy in total doses that may be regarded as safe produces more rapid improvement. Strauss and Kligman[9] made a crucial histologic study to determine the amounts of irradiation necessary to produce a decrease in size and function of sebaceous glands. *Single* doses of 800 to 1200 r in air produce significant reduction in the size of a sebaceous gland but at the cost of severe adverse changes in the connective tissue of the corium. Within a few weeks the sebaceous gland *returns to its original size*; permanent reduction is not achieved. This finding is, I submit, a convincing refutation of the long-held clinical belief that x-rays have a sufficiently selective effect on the sebaceous gland to be effective in acne without the risk of damage to connective tissue, blood vessels, nerves, and other ancillary glands.

Since 1942 I have employed x-ray therapy in almost no cases of acne, and since 1948 I have not used it at all in this condition. I shall never use it again for acne.

Psoriasis—The effects of x-rays in psoriasis are unpredictable; sometimes they are temporarily gratifying but often they are not. In our experience, except for lesions with thick scales, very soft (half-value layer of 0.035 mm. aluminum) rays are fully as beneficial as harder rays and much safer for vital underlying structures.

Acute contact dermatitis (dermatitis venenata)—X-ray therapy is worthless.

Chronic eczematous dermatitis—The effectiveness of x-ray therapy is unpredictable. If multiple lesions are present, its usefulness should first be determined in single areas. Very soft rays are preferable.

Keloid—I have never observed any good effect from x-rays on a typical well-established

keloid. Most reports of good effects, in my opinion, have been based on the observation of temporarily hypertrophic scars, which will respond as well or better to intracutaneous injection of a corticosteroid or, for that matter, to the passage of time.

Herpes simplex—X-ray therapy is probably ineffective and certainly not justified.

Herpes zoster—There is no convincing evidence of the effectiveness of x-ray therapy in herpes zoster, either to individual lesions or to the affected nerve roots.

Warts—X-ray therapy in large "tumoricidal" doses is never justified. In plantar warts on pressure points, a "perfect" result often is succeeded years later by a scar far more troublesome and painful than the original lesion.

Hemangioma—This is by far the most controversial benign condition in respect to x-ray therapy. I am regularly astonished by the completely divergent advice given to parents. My colleagues and I[10] have discussed this problem extensively in another publication. Suffice it to say here that hemangiomas composed of "mature" vascular and other tissue elements (port-wine stains, cavernous hemangiomas) are *not* radiosensitive. For "immature" hemangiomas, which appear or enlarge after birth and subsequently disappear spontaneously, competently administered radiotherapy in modest doses may be justified occasionally but by no means routinely.

Ringworm infections—One of the chief boons of griseofulvin is that it has made x-ray epilation for tinea capitis passé. In ringworm infections of other areas, x-ray therapy can add little.

A Potential Threat to Medicine

I am impelled to add a most sober warning. The climate of opinion on the dangers of ionizing radiation from any source, among the lay public, among public health authorities, and even in Congress, is such that abuse of such therapy may not long be tolerated, even the relatively isolated current pattern of such abuse. This misuse constitutes a potential threat to the good name of medicine in general and to the specialties chiefly responsible for dispensing x-ray therapy in particular. These specialties should redouble their campaigns of education, study and self-regulation.

Regulation of x-ray therapy may be forced on us by outside agencies. There can be no question of the need for licensing and surveillance of every x-ray unit in the United States. Total elimination of such therapy for benign diseases may well occur if abuses are not stopped.

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Severe Toxemia of Pregnancy

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A simple program of treatment is outlined which has proved highly successful in the management of more than 400 cases of severe toxemia of pregnancy, including 73 cases of eclampsia. A combination of cryptenamine and hydralazine is given intravenously to reduce vasospasm, and magnesium sulfate is given intramuscularly for sedation.

MILTON L. MCCALL

TOXEMIA of pregnancy still ranks high as a cause of maternal and fetal deaths, having accounted directly or indirectly for more than 35,000 perinatal casualties in the United States in 1959. The incidence is highest in the deep South, but fulminating toxemia is seen occasionally even in the most carefully regulated practices in the North, and any physician whose practice includes obstetric patients must be able to approach its management intelligently. Enough progress has been made so that treatment usually can be successful, and it is certainly not true that we are helpless to overcome the high maternal and fetal mortality rates.

The cause of toxemia of pregnancy is unknown. The disease is characterized by hypertension, albuminuria, edema, excessive weight gain, and various subjective symptoms ranging from headache to epigastric pain. The impact on the nervous system may be severe, resulting in the convulsions and coma of eclampsia.

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Research related to toxemia of pregnancy has produced some spectacular developments recently. For example, Hunter described a substance, "hysterotonin," found in the decidua and amniotic fluid which causes vasoconstriction and can reproduce the clinical picture of toxemia of pregnancy. When amniotic fluid is withdrawn through the abdominal wall, the toxemic state frequently improves. The same effect is achieved by dilatation and curettage after delivery and removal of the decidua. Although this research is very promising, we had better wait for complete confirmation before incorporating these developments in our therapy.

Keener insight into the physiologic and pathophysiologic aspects of the disease, of course, has brought about the most significant developments. There is better understanding of blood flow to the liver, kidneys and brain; we know more about the hemodynamics of the heart and circulatory system. Thus we have a more solid footing on which to base

medical treatment and also have some assistance in the fine timing that is so important in relation to interruption of pregnancy.

When many of you went to medical school, and certainly when I did, what we were taught concerning toxemia of pregnancy was derived at the autopsy table from a patient who had died from eclampsia. The findings were periportal necrosis of the liver, a little thickening of the glomerular membrane of the kidney, a few petechial hemorrhages, occasionally some edema of the brain, and that was it. These findings were helpful but hardly told the complete story; they represented the debris and chaos remaining after the storm had passed. Today we are better able to understand the current of abnormal function "at the height of the hurricane."

The Hypertensive Crisis

In toxemia of pregnancy, fundamental changes take place in each organ of the body; in addition, there are general effects such as retention of water and sodium, vasospasm, significant hormonal alterations, and hematologic disorders. The most important considerations in regard to the hypertensive crisis of severe toxemia are the specific pathophysiologic effects on the brain, kidney and heart and the significant general changes such as vasoconstriction, anoxia, and hyperirritability of the nervous system.

What does vasoconstriction do? This phenomenon, which occurs in the small arterioles and to some degree in the precapillary vessels, increases vascular resistance and brings about the hypertension that is so typical of toxemia. The hypertension increases intravascular pressure and predisposes to hemorrhage in major areas of the body. The brain, in particular, cannot well withstand such insults. Moreover, the heart itself is subjected to a greater work load. Early in the third trimester, cardiac output already is increased, and there is, therefore, a threat of heart failure due to the increased vascular resistance and hypertension and to the effects of anoxia as the disease worsens.

At least two kinds of anoxia are present in the most severe stage of toxemia, which is eclampsia. One is anoxic anoxia due to disturbance of respiration during convulsions. The other type is associated with the coma between convulsions; it is not anoxic anoxia, since there is no desaturation of the hemoglobin with oxygen. The cells themselves are unable to pick up oxygen as well, and the state is similar to histotoxic anoxia.

As the disease becomes more critical, irritability of the nervous system is evident. The patient becomes restless, reflexes are hyperactive, and finally convulsions occur.

Management

Management of severe toxemia of pregnancy is a complex problem. We must endeavor to relax vasospasm without interfering with organic blood flow. In recent years we have learned that some hypotensive (vasodilator) drugs will do this gracefully and others will not. We must control the hyperreactivity of the nervous system (to control or prevent convulsions) without overdepressing the patient and her vital metabolic and circulatory functions.

Patients with severe toxemia of pregnancy often are overtreated. Sedatives in huge amounts, so commonly employed, are contraindicated. We have shown that these agents, especially the intravenously administered barbiturates, cause ischemia of the brain and aggravate the anoxia already present. We have come to use a combination of therapeutic measures that precludes such basic physiologic alterations, prevents prolonged coma, and lowers mortality and morbidity for both mother and baby.

It became evident in our research that no sedative could be regarded as a good vasodilator as well. The barbiturates such as AMYTAL® and PENTOTHAL®, when introduced into the blood stream, interfere with vital bodily function. It was mandatory to find a good sedative that would not overdepress the mother, compromise cerebral, renal or cardiac function, depress the fetus, or interfere with normal labor. Magnesium sulfate was found to approach this ideal most closely.

To mild, safe sedation, we added infusion of vasodilators to relax vasospasm without interfering with hemodynamics. Many drugs

were studied, and the ideal combination from the standpoint of over-all homeostasis was found to be UNITENSEN® (cryptenamine) and APRESOLINE® (hydralazine). The therapy to be described has been used routinely in more than 400 cases of toxemia of pregnancy with severe hypertensive crisis, including 73 cases of eclampsia; only one patient has died.

1. A mixture of 20 mg. Apresoline and 5 mg. Unitensen in 500 cc. of 10 or 20 per cent solution of glucose is attached to one limb of a Y tube.

2. Plain glucose solution is attached to the other limb of the Y tube.

3. Intravenous infusion of the vasodilator mixture is started at 20 drops per minute.

4. Blood pressure readings are taken every five minutes for the first two hours and every 15 minutes thereafter.

5. The inflow of the vasodilator infusion is regulated as necessary after each blood pressure reading to maintain the pressure at a steady level (110 to 140 mm. Hg systolic, 60 to 90 mm. Hg diastolic).

6. If systolic blood pressure falls to less than 100 mm. Hg, the vasodilator infusion is discontinued temporarily and the plain glucose solution is substituted until the pressure rises to the desired level.

7. If medical induction of labor is desirable, a third bottle containing a dilute oxytocic mixture is added.

8. If blood pressure does not fall in 30 to 45 minutes when the infusion is given at a rate of 60 drops per minute or more, 1 mg. of Unitensen should be added for each 100 cc. of solution (usually 5 mg.).

In addition, 20 cc. of 50 per cent magnesium sulfate is injected intramuscularly in the buttocks (half in each side). Injections of half this dosage may be repeated as necessary, as long as urinary output is good (more than 800 ml. in 24 hours), patellar reflexes are present, and the respiratory rate is more than 14 per minute. Very occasionally, 16 mg. morphine sulfate (¼ gr.) and 0.4 gm. sodium phenobarbital (5 gr.) may be given intramuscularly (never intravenously); but when the patient is in labor, and on most other occasions, magnesium sulfate is preferred.

This combination treatment is used for patients who exhibit a sudden rise in blood pressure during labor, all patients with eclampsia whose systolic blood pressure is 150 mm. Hg or higher, patients with preeclampsia who do not respond to routine conservative therapy, those with hypertension and superimposed preeclampsia, and those with a sudden and appreciable rise in blood pressure post partum.

The aims of therapy are as follows:

1. To afford at least temporary relief from intense vasospasm and the damage it inflicts.

2. To ensure maintenance of normal visceral circulation and function through the action of Apresoline on the kidney combined with over-all maintenance of homeostasis in other vital organs with Unitensen.

3. To gain valuable time to study and evaluate the patient under less threatening circumstances than otherwise would be possible, while preparations are being made for the more definitive therapy of interrupting pregnancy.

4. To circumvent the necessity of using large amounts of sedatives or conduction anesthetics and their harmful effects.

Use of this therapy should be continued for from 12 to more than 100 hours, as indicated.

On our service in the South, before I came to Pittsburgh in 1959, almost 9000 of 51,000 obstetric patients delivered at the hospital had toxemia of pregnancy. Only the patients with the most severe disease were given vasodilators, and this therapy lowered the blood pressure to normal levels and also effected a notable decrease of albuminuria (which usually was 4 plus). In the 10 years prior to 1955, toxemia of pregnancy was the most common cause of maternal death; 47 per cent of the deaths were due to gross cerebral hemorrhage. In the five years after institution of the combination therapy described, there was only one death from toxemia and there were no cerebral hemorrhages as far as could be determined.

While it is true that severe hypertensive crisis or eclampsia or both are not everyday occurrences in the North, it is evident that such complications still may confront us. The comparatively simple therapy outlined herein has proved highly successful and is recommended to each of you.

Office Diagnosis of Congenital Malformations of the Heart, Part 2

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In part 1 of this discussion, published last month, the authors discussed acyanotic malformations including ventricular septal defect, patent ductus arteriosus, atrial septal defect, pulmonary stenosis, aortic stenosis, and aortic coarctation. The cyanotic entities described in part 2 include tetralogy of Fallot, transposition of the great vessels, tricuspid atresia, and Ebstein's anomaly.

Cyanotic Congenital Malformations of the Heart;
1. Tetralogy of Fallot

TETRALOGY of Fallot is the most common cyanotic congenital malformation of the heart. The basic elements of this complex are a large ventricular septal defect which approximates the aortic orifice in size and pulmonary stenosis which usually is infundibular in type; rarely it is infundibular and valvular, or valvular alone. Although the aorta overrides the septal defect in most cases, the amount of right-to-left shunting depends primarily on the severity of the pulmonary stenosis. The clinical cases may be divided into three types: (1) the average type of tetralogy, (2) severe tetralogy, and (3) atypical or "acyanotic" tetralogy.

The clinical manifestations of the average type of tetralogy of Fallot are not evident in the first few months of life but become apparent later during the first or second year and usually progress in severity over the subsequent years. Growth and physical development frequently are retarded, activity is limited, and the characteristic history of squatting almost always can be obtained. Clubbing, which usually does not become apparent until the end of the first year, and polycythemia are proportional to the severity of the cyanosis. Heart size is not appreciably enlarged although a lower parasternal lift is present indicating right ventricular enlargement. A grade 3 to 4 murmur which is not pansystolic and frequently is accompanied by a thrill is located maximally over the third left sternal

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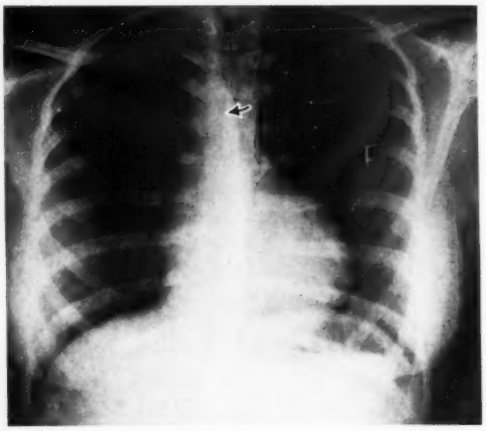

FIGURE 9. Posteroanterior chest roentgenogram of 13 year old girl with tetralogy of Fallot. The heart size is within normal limits and the esophagus is pushed to the left (arrow) by a right aortic arch. Pulmonary vascular markings are diminished.

space and is well transmitted to the second and fourth left interspaces. The second sound over the pulmonary area is loud and single in almost all cases and is due to the aortic valvular closure only. The pulmonary component of the second sound usually is not heard because closure occurs under low pressure and because the pulmonary blood flow is markedly diminished. Roentgenologic examination of the chest reveals a normal transverse diameter of the heart with an elevated apex in the posteroanterior view. In the oblique view the outflow tract of the right ventricle may be more convex and appear closer to the anterior chest wall. The peripheral lung fields are avascular, and a concavity in the region of the pulmonary trunk very frequently is observed, although this may not always be evident, particularly in infants and young children, because of superimposition of the thymus gland (figure 9*). When the stenosis involves the pulmonary valves the main pulmonary arterial segment appears straight or even convex due to poststenotic dilatation of the pulmonary artery.

Although these are the typical roentgenologic findings in tetralogy of Fallot, many patients with this anomaly have chest roentgenograms that appear to be within normal limits.

The typical electrocardiogram shows right ventricular hypertrophy of the adaptation type (figure 2, upper tracing). In young infants who are still acyanotic and in whom the clinical findings simulate those of ventricular septal defect, the electrocardiogram is most helpful, since very frequently it shows upright T waves in the right precordial tracings, which after the first week of life almost always indicate right ventricular hypertrophy. When this type of tracing is obtained in an infant who has what appears to be a small, uncomplicated ventricular septal defect, tetralogy of Fallot should be considered seriously.

In severe tetralogy due to marked pulmonary stenosis or even pulmonary atresia, to which the confusing term "pseudotruncus" has been applied, cyanosis is noted shortly after birth and progresses during infancy, with early appearance of clubbing. Cerebral hypoxic spells, often precipitated by crying or feeding and characterized by dyspnea, marked cyanosis and temporary loss of consciousness, are common and indicate the severity of the malformation. Examination of the heart reveals a definite left lower parasternal lift, a loud and single second sound in the pulmonary area due to the aortic valvular closure, and a faint, short, grade 2 ejection systolic murmur at the base. In rare instances there may be no murmur at all, indicative of the severe obstruction to pulmonary blood flow. There is no murmur from the ventricular septal defect because of the equivalent pressures of the right and left ventricles. An early systolic click of aortic origin is common at the apex and at the aortic area, and this probably is due to the dilatation of the ascending aorta. Chest roentgenograms and electrocardiograms are similar to those in type 1 except for marked avascularity of the lung fields. If untreated, these patients usually die during infancy.

In the relatively few patients who have so-called acyanotic tetralogy of Fallot, a mild degree of pulmonary obstruction is present and the elevated right ventricular pressure is

*Figures 1 through 8 appeared in part 1, which was published last month.

still lower than the systemic level so that only a left-to-right shunt occurs through the septal defect. The patients usually are asymptomatic and have no cyanosis, although marked exertion may precipitate transient episodes of cyanosis. Growth and development may proceed relatively normally for many years. Heart size is within normal limits or may be increased. A systolic thrill is present in the left sternal border. The first sound is normal, and the second sound is either widely split with a diminished pulmonary component or single with only the aortic closure audible. A grade 3 to 4 ejection systolic murmur is present at the pulmonary area, and a pansystolic murmur of similar intensity but somewhat higher-pitched is present, maximally heard at the fourth left sternal space. The systolic ejection murmur at the base characteristically diminishes in intensity immediately following inhalation of amyl nitrite, in contrast to the increased intensity response in pulmonary stenosis with intact ventricular septum. This simple test is very useful in clinical differentiation of the two entities. Chest roentgenograms reveal some increase in pulmonary vascular markings and mild cardiac enlargement involving both ventricles and sometimes accompanied by mild left atrial enlargement. The electrocardiogram usually shows biventricular hypertrophy.

The clinical features associated with small or moderate-sized uncomplicated ventricular septal defects (groups 1 and 2) resemble to some extent the findings just described. There is, however, only one type of murmur present, the typical harsh pansystolic murmur at the third and fourth left sternal spaces, and the second sound normally is split. The electrocardiogram is normal or may show only left ventricular hypertrophy.

Severe pulmonary stenosis with intact ventricular septum and right-to-left shunt at the atrial level should always be considered in the differential diagnosis of tetralogy of Fallot. The patients also may be cyanotic and symptomatic. However, congestive heart failure commonly develops in these young patients, and it rarely if ever develops in uncomplicated tetralogy. The heart is markedly enlarged and the typical prolonged stenotic murmur and very wide splitting of the second sound described for isolated pulmonary stenosis are present. Although the pulmonary component of this widely split second sound is diminished in intensity, only very rarely is it inaudible, and even then it is still recognizable in the phonocardiogram. Poststenotic dilatation of the pulmonary trunk is far more common in this entity than in tetralogy. The electrocardiogram usually shows severe right ventricular hypertrophy of the barrage type (figure 2, lower tracing).

2. *Transposition of Great Vessels*

Complete transposition of the great vessels as a cause of cyanosis during infancy is second in frequency only to tetralogy of Fallot. It is the most common cause of cyanosis in the neonatal period. In its usual form the chambers of the heart are positioned normally and the aorta originates from the right ventricle and the pulmonary artery from the left ventricle. The resulting complete separation of the venous and arterial routes of blood flow is incompatible with life unless a communication exists between the systemic and pulmonary circuits. The common additional anomalies are ventricular septal defects, atrial septal defects or patent foramen ovale and patent ductus arteriosus, singly or in combination. The clinical picture may be divided into two types, depending on the presence or absence of pulmonary stenosis.

In complete transposition of the great vessels without pulmonary stenosis (the common type), cyanosis is present at or shortly after birth and very quickly becomes pronounced. Dyspnea is prominent; weight gain and physical development are retarded. The heart rapidly increases in size with dilatation of all chambers, particularly the right atrium and right ventricle. The second sound is accentuated over the pulmonary area and may be closely split or single. There may be no murmurs; if present, they are due to the associated defects. Cardiac enlargement with an "egg-shaped" contour usually is characteristic in the posteroanterior view, as well as the narrow base which appears wider in the oblique roentgeno-

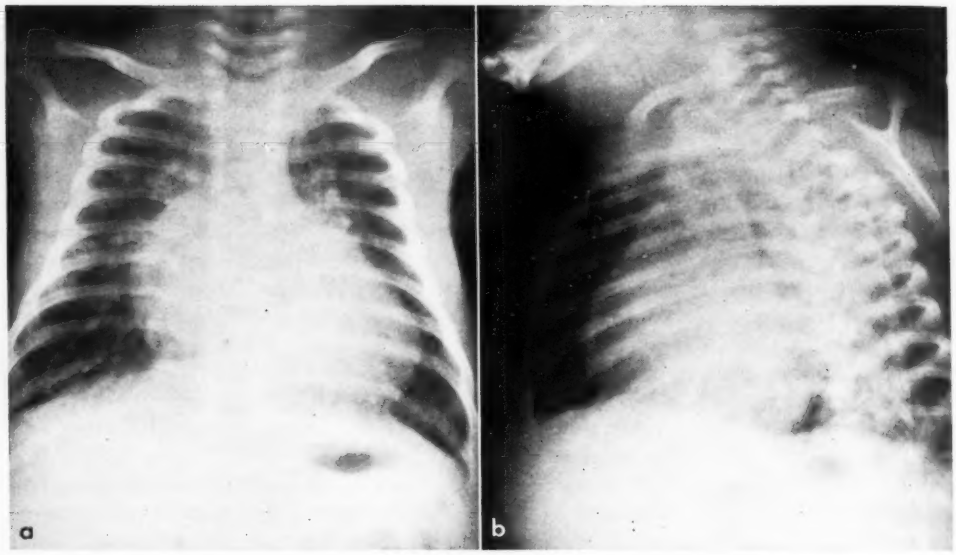

FIGURE 10. Chest roentgenograms of a one month old boy with complete transposition of the great vessels.

a. Posteroanterior view showing the characteristic "egg-shaped" configuration, a narrow base, and increased pulmonary vascular markings.

b. Left anterior oblique view. The base is wider than in the posteroanterior view.

grams of the chest (figure 10). Not uncommonly, fluoroscopic examination reveals what appears to be diminished pulmonary vascular markings and pulsations, but in the chest roentgenograms the markings and pulsations are increased. The electrocardiogram usually shows right atrial and right ventricular hypertrophy. The vast majority of these patients die during infancy. Some live a number of years; we have seen one proved case of this anomaly in which the patient was in the fifth decade of life.

In transposition of the great vessels with pulmonary stenosis, the pulmonary blood flow is diminished. The patients are less dyspneic than those who have transposition without pulmonary stenosis, and the heart size is smaller, although they are similarly cyanotic right after birth. Clinical findings are almost identical to those described for severe tetralogy of Fallot, consisting essentially of left lower parasternal lift, a single loud second sound of aortic origin, and a harsh, grade 3 to 4 ejection systolic murmur at the base, sometimes louder at the aortic than at the pulmonary area. Chest roentgenograms reveal the "egg-shaped" contour with a narrow base in the posteroanterior view and diminished pulmonary vascular markings. The electrocardiogram shows right atrial and right ventricular hypertrophy and occasionally biventricular hypertrophy.

The Taussig-Bing anomaly is closely related to complete transposition of the great vessels. The aorta originates from the right ventricle and the pulmonary artery is levoposed, i.e., it overrides both ventricles above a large ventricular septal defect. These patients are not as cyanotic as patients with complete transposition of the great vessels without a ventricular septal defect, and they live longer. Clinical auscultation does not distinguish this entity from complete transposition with ventricular septal defect. Roentgenologically, however, a bulge of the pulmonary area is more common in Taussig-Bing anomaly than in complete transposition of the great vessels. Pulmonary vascular markings and pulsations also are in-

creased. A definite differential diagnosis between these two entities sometimes may be established by means of angiocardiography. In Taussig-Bing anomaly the aorta is not displaced far anteriorly as it is in complete transposition of the great vessels. From the standpoint of prognosis and present-day treatment, differentiation of these two entities appears to be more of academic than of practical interest.

It should be emphasized that corrected transposition of the great vessels is a distinct entity, totally unrelated to complete transposition of the great vessels and with completely different hemodynamics. Inversion of the ventricles is present so that the pulmonary artery receives venous blood from the anatomic left ventricle and the aorta receives oxygenated blood from the anatomic right ventricle. This alone does not produce a physiologic abnormality, but additional malformations are very commonly associated with corrected transposition, the most frequent being ventricular septal defect, congenital deformity of the mitral valve producing mitral regurgitation, and pulmonary stenosis. Clinical, roentgenologic and electrocardiographic findings depend on the associated lesion. A first-degree atrioventricular block is commonly noted in the electrocardiogram. Because of the reversed relationship of the great vessels, the second sound may appear abnormal. The usual splitting of the second sound may be audible at the aortic area instead of at the pulmonary area where it normally occurs. At the pulmonary area the second sound is single and very loud because of the close proximity of the aortic root to the anterior chest wall. This finding may lead the clinician to an erroneous diagnosis of pulmonary hypertension. Although a few roentgenologic signs have been described in the literature, we have not found any that can be considered strongly suggestive of this condition. A definite diagnosis is best established by means of biplane angiocardiography.

3. Tricuspid Atresia

Congenital atresia of the tricuspid valve, which is always accompanied by an interatrial communication and by hypoplasia of the right ventricle, usually is manifested by the appearance of cyanosis at birth or in early infancy. The pulmonary artery usually is hypoplastic. The left heart chambers fill by way of the interatrial communication, whereas filling of the right ventricle and pulmonary vessels depends on a ventricular septal defect or patent ductus arteriosus and partly on bronchial arterial blood flow. Although an occasional patient with tricuspid atresia may live for several years or rarely even as long as early adulthood, the vast majority of such patients die during infancy.

The characteristic clinical features are cyanosis in early infancy, roentgenologic evidence of enlargement of right atrium and left ventricle with diminished pulmonary vascular markings, and electrocardiographic findings of right atrial and left ventricular hypertrophy. The second sound over the base is frequently single because only aortic closure is audible. A fourth heart sound may be present, sometimes accompanied by prominent "a" waves in the neck veins and by presystolic pulsations in the liver in cases in which only a small patency of the foramen ovale is present. There may be no murmur, or a grade 3, harsh systolic murmur may be present in the third and fourth left sternal spaces if a ventricular septal defect exists. The heart is mildly to moderately enlarged in the chest roentgenograms. The right heart border in the posteroanterior view is prominent due to right atrial enlargement; the left lower heart border is unusually wide and convex due to left ventricular enlargement, and the upper left medial border may be convex due to left atrial enlargement. In the typical cases the anterior cardiac shadow in the left anterior oblique view appears to have been "chopped off" due to the hypoplastic right ventricle. The pulmonary vascular markings are diminished (figure 11). The electrocardiogram characteristically shows left axis deviation, right atrial hypertrophy and left ventricular hypertrophy (figure 12).

Tricuspid atresia occasionally may be accompanied by complete transposition of the great vessels. The pulmonary artery which arises from the left ventricle usually is dilated

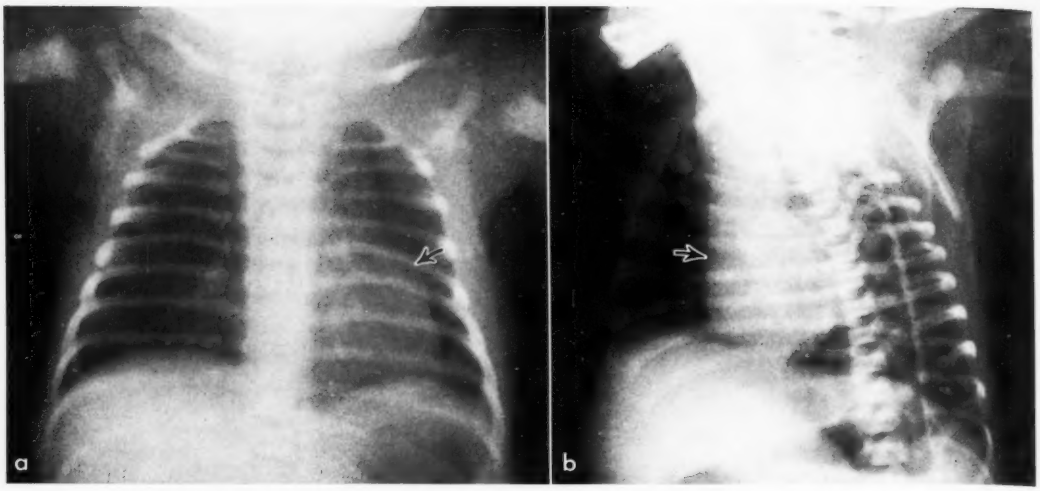

FIGURE 11. Chest roentgenograms of a one week old boy with tricuspid atresia.

a. Posteroanterior view showing slight cardiac enlargement, convexity of the upper left medial border due to left atrial enlargement (arrow), and diminished pulmonary vascular markings.

b. Left anterior oblique view. The anterior cardiac border is vertical and "chopped off" (arrow) due to the marked hypoplasia of the right ventricle.

and the pulmonary blood flow is increased. The aorta which arises from the hypoplastic right ventricle is hypoplastic, and preductal coarctation may be present. Because of the abundant pulmonary blood flow, the infants are only mildly cyanotic but they very often have tachypnea, dyspnea and frequent respiratory infections. The heart is larger than it is in tricuspid atresia without complete transposition of the great vessels, and the enlargement similarly involves the right atrium, left atrium and left ventricle. A grade 3 to 4 systolic murmur in the lower precordial area also is noted, and the rest of the physical findings described previously are present. Fluoroscopic and roentgenologic examination of the chest reveals marked dilatation and pulsation of the pulmonary trunk and its primary branches, increased pulmonary vascular markings, and right atrial, left atrial and left ventricular enlargement. The electrocardiogram is similar to that in the preceding type (figure 12).

4. Ebstein's Anomaly

Ebstein's anomaly of the heart is characterized by marked deformity and downward displacement of one or more tricuspid valves into the right ventricle. The portion of the right ventricular wall proximal to the displaced valves becomes incorporated into the right atrium, with consequent reduction in volume and functional capacity of the right ventricle. The tricuspid valves frequently are incompetent. Many patients have an interatrial communication through which right-to-left shunting eventually takes place as right atrial pressure increases.

The usual clinical course is one of progressive disability, the most common symptoms being fatigability, exertional dyspnea and mild cyanosis. A number of these young patients, however, present no disability or cyanosis but have paroxysmal attacks of supraventricular tachycardia. On examination the symptomatic patients have mild cyanosis and marked cardiomegaly with a remarkable absence of left lower parasternal lift. The area of cardiac dullness in the right heart border is increased due to right atrial enlargement. A triple or, rarely, quadruple rhythm is a nearly constant finding due to diastolic extra sounds heard over the precordium which

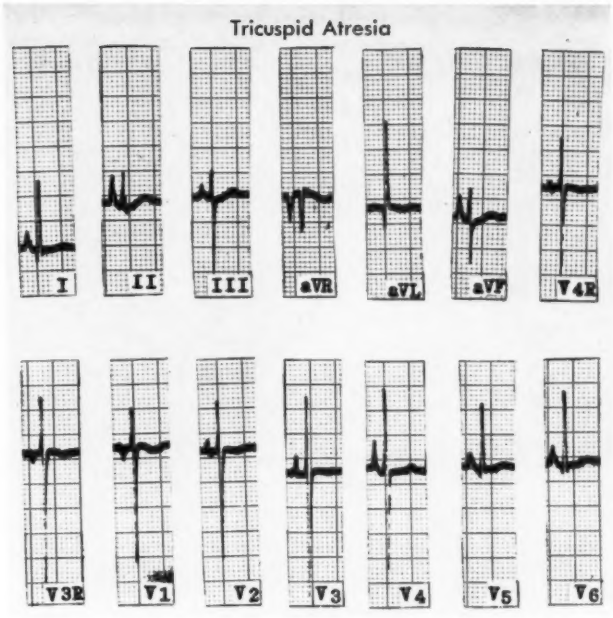

FIGURE 12. Electrocardiogram of one month old girl with tricuspid atresia demonstrating the typical left axis deviation, horizontal electric position, tall and peaked P waves due to right atrial hypertrophy, and left ventricular hypertrophy.

closely resemble the third or fourth heart sounds except that they are higher-pitched and of wider distribution. A systolic murmur accentuated during inspiration usually is present, and frequently is heard best near the apex due to the abnormal location of the tricuspid valves. This systolic murmur is attributed to tricuspid regurgitation. At times, a faint, superficial and "scratchy" mid-diastolic or presystolic murmur is audible over the lower precordial area which may originate from the malformed tricuspid valves. Roentgenologic examination of these symptomatic patients reveals moderate to marked cardiac enlargement with prominent right and left heart borders and diminished vascularity of the lung fields. The right atrium is enlarged to a considerable degree. The electrocardiogram characteristically shows right bundle-branch block and tall, peaked P waves in the right precordial tracings indicative of right atrial hypertrophy. A prolonged P-R interval is common. The diagnosis almost always can be made by the auscultatory, roentgenologic and electrocardiographic findings we have described.

5. *Total Anomalous Pulmonary Venous Connection*

Anomalous pulmonary venous connection may be total or partial. In the partial type, some of the right pulmonary veins enter the superior vena cava or the right atrium, and the functional disturbance consists essentially of a left-to-right shunt at the atrial level. Clinical and hemodynamic findings are identical to those in uncomplicated atrial septal defect.

In total anomalous pulmonary venous connection, no veins enter the left atrium. The systemic venous blood and the fully oxygenated blood from the pulmonary veins enter and mix in the right atrium. An atrial communication is present (either a patent foramen ovale or an atrial septal defect) which permits blood to reach the left heart and systemic circulation. The anomalous venous connection may be into the supradiaphragmatic structures (left innominate vein, superior vena cava, right atrium, coronary sinus, azygos veins) or into the infradiaphragmatic structures (portal vein or tributaries, ductus venosus, inferior vena cava).

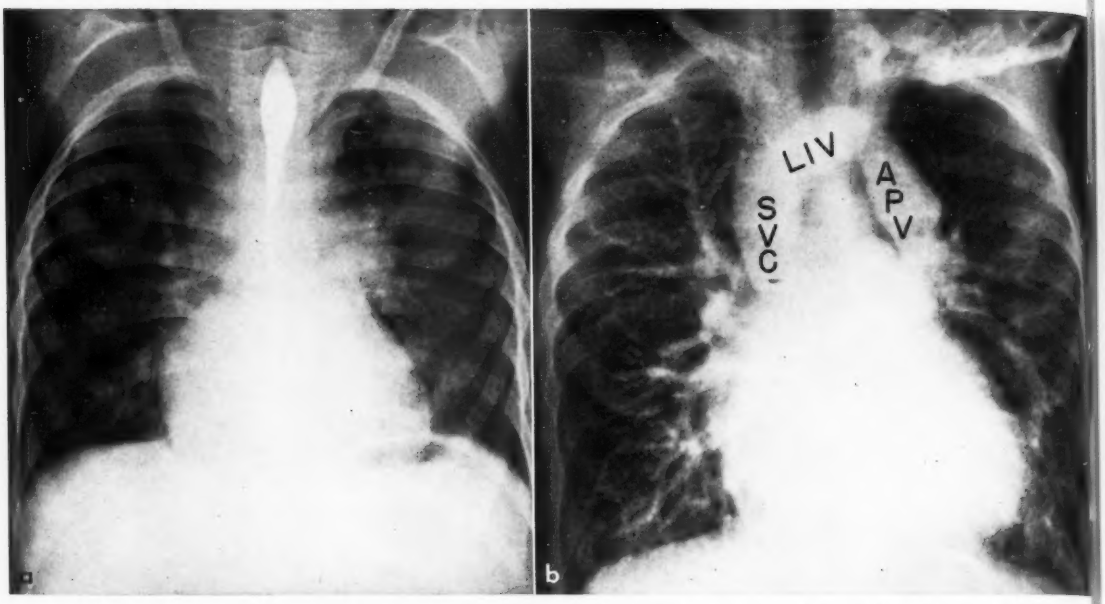

FIGURE 13. Posteroanterior chest roentgenogram and angiocardiogram of seven year old boy with total anomalous pulmonary venous connection to the left innominate vein.

a. Chest roentgenogram demonstrating the characteristic figure-of-eight configuration and the increased pulmonary vascular markings.

b. The venous angiocardiogram shows the position of the anomalous pulmonary venous trunk (APV) on the left side and the dilated superior vena cava (SVC) on the right side. LIV designates the left innominate vein.

The supradiaphragmatic type of total anomalous pulmonary venous connection is far more common than the infradiaphragmatic type. The most common site of anomalous connection is the left innominate vein, followed in order of frequency by the superior vena cava, right atrium and coronary sinus. Unless a significant atrial septal defect is present, patients with this malformation die during infancy. Because of the abundant pulmonary blood flow, they are very dyspneic, and unless they are in the preterminal state they are only slightly cyanotic. A left lower parasternal lift is present which indicates right ventricular hypertrophy. An unusually loud and easily palpable first heart sound inside the apex is present due to rapid and forceful tricuspid valvular closure from the increased flow through the tricuspid orifice. A loud third heart sound and a mid-diastolic rumble inside the apex are similarly explained. The second heart sound is accentuated and single or closely split at the base due to the pulmonary hypertension that usually exists. In cases in which the pulmonary veins empty into the superior vena cava or innominate vein, a faint, high-pitched, continuous murmur usually is heard at the base which may be mistaken for a venous hum except that it is not altered by position or by compression of the jugular veins. A grade 2 to 3 ejection systolic murmur is present in the pulmonary area due to increased flow through the pulmonary orifice. Fluoroscopic and roentgenographic examination of the chest reveals right atrial and right ventricular enlargement, dilated and prominently pulsating pulmonary arteries in the medial and midlung fields, and markedly increased pulmonary vascular markings.

If the pulmonary veins enter either the left

innominate vein or the superior vena cava, a characteristic cardiac configuration usually is noted after the age of approximately two months. It consists of a figure-of-eight appearance composed of the cardiac shadow below and the vascular shadows in the supracardiac area above. The latter consists of the anomalous pulmonary venous trunk on the left side and the dilated superior vena cava on the right (figure 13). The electrocardiogram shows marked right axis deviation, right atrial hypertrophy and severe right ventricular hypertrophy.

The infradiaphragmatic type of total anomalous pulmonary venous connection is rare. When the pulmonary veins drain into either the portal vein or the ductus venosus, the infants usually die within the first month of life. Cyanosis and respiratory distress appear at or shortly after birth. The heart is not enlarged appreciably, and there are no unusual auscultatory findings. In the chest roentgenograms the heart size is within normal limits, and the lung fields have a diffuse reticulated appearance due to blood stasis secondary to the obstruction to pulmonary venous return in the liver. The electrocardiogram reveals right ventricular hypertrophy.

A few complex anomalies whose clinical and hemodynamic features resemble those of total anomalous pulmonary venous connection are cor triatriatum, mitral atresia or severe mitral stenosis, and hypoplasia of the aortic tract complex. These conditions manifest congestive heart failure in infancy, marked right ventricular enlargement and pulmonary hypertension, marked cardiomegaly with dilated pulmonary trunk and increased pulmonary vascular markings in the chest roentgenograms, and severe right ventricular hypertrophy in the electrocardiogram. Cardiac catheterization and selective angiocardiography are necessary to differentiate these entities from total anomalous pulmonary venous connection as well as from one another, and in some cases it is not possible to make the distinction even when these special diagnostic procedures are used.

Summary

1. Two hundred and ninety-six patients with congenital malformations of the heart were seen in office consultation in 1959. The clinical diagnosis in each case was based on history, physical examination, fluoroscopic or roentgenographic examination of the chest (or both), and electrocardiograms. Of these 296 cases, a final diagnosis was established in 129 by additional studies (angiocardiography, cardiac catheterization, surgery or autopsy). The office diagnosis in these 129 cases was correct in 94 per cent (122 cases).

The following entities, in order of frequency, accounted for about 90 per cent of cases of congenital malformations of the heart seen in office consultation: ventricular septal defect, innocent murmur, tetralogy of Fallot, atrial septal defect, pulmonary stenosis with intact ventricular septum, aortic stenosis, patent ductus arteriosus, transposition of the great vessels, Ebstein's anomaly, and coarctation of the aorta.

2. A review of the hospital records of 180 patients with congenital malformations of the heart admitted to the cardiology department of Cook County Children's Hospital in 1959 disclosed that the diagnosis was established in 155 of the cases by angiocardiography, cardiac catheterization, surgery or autopsy. The clinical diagnosis in these 155 cases was correct in 90 per cent (139 cases).

The following entities, in order of frequency, caused about 90 per cent of the 180 hospital cases: ventricular septal defect, tetralogy of Fallot, fibroelastosis, patent ductus arteriosus, common atrioventricular canal, pulmonary stenosis with intact ventricular septum, aortic stenosis, ventricular septal defect and pulmonary stenosis, ventricular septal defect and patent ductus arteriosus, Taussig-Bing anomaly, coarctation of the aorta, coarctation of the pulmonary artery, tricuspid atresia, Marfan's syndrome with aortic sinus aneurysm, and atrial septal defect.

3. The salient points in the clinical diagnosis of the common entities are discussed.

Primal Anxiety and Psychiatric Emergencies

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Psychiatric emergencies occur when anxieties and tensions overwhelm a weak or exhausted ego and result in irrational fight-flight reactions. The key to understanding, preventing and treating these conditions rests centrally with primal anxiety. Recognition of this mental state before the acute disruptive episode, which may lead to suicide, murder, acute psychosis or group panic, is important, and family physicians are in a favorable position to meet the situation before tragedy supervenes. The distinguishing characteristics of normal anxiety, secondary anxiety and primal anxiety are presented, and symptoms and methods of handling situations seen often by the family physician are outlined.

A PHYSICIAN who only rarely sees a patient with a psychiatric emergency may, like an efficient skipper of a ship, hold his group steady, and the group may handle its problems with few acute breakdowns. Another physician may never see a psychiatric emergency because he personally avoids such a situation by practicing in such a way that he does not become involved therein; patients sense this, and find someone else to help them. Between these extremes are those situations which surprise us, when patients unexpectedly become psychotic or attempt suicide—when we realize we have "missed the boat." Something has been going on that we have not understood. This is most distressing. Or the physician may recognize that a psychiatric emergency is impending and struggle along with the family and the patient, using drugs and medications. Many times he is successful in preventing the acute disruption; other times he fails. This interesting and important problem will occur in the practice of medicine as long as human beings are under pressure. The physician can learn to handle it better.

In psychiatric emergencies the emotion of the physician is involved to a significant and crucial degree. Objective handling is seldom the rule, and frequently he becomes emotionally involved. Because of this, management is uniquely complicated.

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BARNEY M. DLIN

As background, let us describe how our own study on this subject began. A small open-ward psychiatric and psychosomatic inpatient section was set up in Temple University Hospital, without locks or bars, for "borderline" patients, too sick to be managed as outpatients but not sick enough to require institutionalization. Our staff was psychoanalytically trained, and we began the operation of the facility with great enthusiasm. Occasionally, however, we were surprised to find that a patient who apparently had been doing well would abruptly disappear from the hospital or sign himself out. When this continued to happen, we had to realize that we had failed to understand what was going on, that we were missing something important. Thus began our study to find out exactly what we had missed.

The first time we were successful in anticipating an acute emergency, we reconstructed a very interesting series of events, which we present here in the words of the original report (by Dr. Fischer).

"I was in charge of the ward. I awoke one morning from a very restless sleep. I like to sleep, and I sleep soundly; it bothers me when I don't. At 7 o'clock the phone rang; the call was from an artist on the staff, who said, 'I am worried about Mr. X [a patient]. I couldn't sleep last night; I saw something in his art that disturbed me.' A few minutes later a nurse called to say that Mr. X had disappeared. About half an hour later Mr. X's father called to say that his son had come home, in a disturbed state, and they wished to talk it over. The son said he had been panicky and upset for several days because he was afraid a patient across the hall was going to kill him. We decided that under the circumstances we would transfer him to another treatment facility. About that time, the nurses came in and said, 'We think we want to quit. We don't like taking care of psychiatric patients. It is a most uncomfortable business.' We went to the patient across the hall and asked him how he was feeling. He replied, 'I'm feeling terrible. Haven't you noticed I haven't been out of my room for five days? That fellow who just left here was going to kill me.' "

We never found out who would have killed whom, but we did find a very powerful emotional situation that we had not recognized sufficiently. It is impossible to prevent what is not understood. The episode demonstrated that far more attention and study were needed.

In retrospect, we observed that something had mobilized a primal anxiety. It had involved the physician and the treatment group as well as the patient. The power of this affect proved to be the identical "power" that makes the placebo effective. It involves the same "power" that is mobilized by hypnosis. On another level, the Mary Baker Eddys who start things like Christian Science accomplish something with it; the Billy Grahams influence many with it; Hitler did something with it. *This same powerful primal emotion is a potential of any doctor-patient relationship.* It can help to prevent disruptions, it can treat them, or, unfortunately, in an iatrogenic way, it can make them worse. It is the "power" of change, for better or for worse.

We need something in the area of the psyche that is comparable to the "vital signs" used by the anesthetist during a surgical procedure. Respiration, blood pressure and heart rate tell him whether or not his patient is going to stay alive and do well. What is comparable in the psychobiologic field?

We conclude that prevention and therapy of psychiatric emergency require knowledge of (1) ego function and dysfunction and (2) anxiety levels and types. These are basic "psychic anchorages" in maintaining healthy control and homeostasis. They are basic in preventing a personality disruption. A knowl-

TABLE 1

NORMAL ANXIETY

Characteristics:
Signal of danger
Source of stimulus; reality threat
Leads to appropriate action ("fight-flight")
Action removes or avoids danger
Time: present

Symptoms:
Mental and physical (mild)

Consequences:
Compatible with efficiency
"Valuable experience"

edge of psychodynamics and psychopathology is helpful and preferable, but some psychiatric emergencies can be controlled and prevented with only intuitive interventions.

Ego function and dysfunction will not be emphasized in this discussion. For a presentation of this phase of the subject, the reader is referred to Dr. Karl Menninger's article, "Ego reactions to disintegrative threat," in the *American Journal of Psychiatry* (108:8, 1952). We will focus attention on the psychobiologic levels of anxiety and the various types of clinical anxiety, emphasizing primal anxiety. Let us begin with an "operational" and clinical psychobiologic classification.

Psychobiologic Classification of Anxiety

The classification used here involves a different perspective than dynamic descriptive classifications such as castration or injury anxiety, separation anxiety, birth anxiety, death anxiety, and so on. The dynamic descriptions are useful in other aspects of psychotherapy. The present classification divides anxiety into three types: (1) normal, (2) secondary and (3) primal.

Normal Anxiety

Normal anxiety is a signal of danger (table 1). It indicates that something threatens. There is always a present reality stimulus for it, although the stimulus may not be determined and recognized immediately. The danger and the discovery of the stimulus lead to appropriate action which generally can be termed "fight" or "flight." In the normal person, "fight" may be constructive. It means that he neutralizes or gets rid of the danger. "Flight" means that he runs away from it.

This episode of stress and reaction occurs in the present time, and symptoms involve both mental and physical spheres. In the body there is mild discomfort. In the mind there is an attempt to identify correctly the source of the danger and decide what to do about it. The consequence is that normal anxiety and discovery of the danger are compatible with high physical and mental efficiency. Well-trained athletes experience some normal anxiety before a game; actors experience it before a performance; a physician may experience it before an important operation. Normal anxiety does not interfere with good intellectual or physical function.

Sometimes, normal anxiety occurs immediately after the episode has been completely and satisfactorily resolved. Then it is short-lived and does not cause any trouble. Successful handling of normal anxiety is a valuable experience, although one may not wish to repeat it. It is compatible with and accompanies growth and maturity.

Secondary Anxiety

Secondary anxiety is pathologic (table 2). It may occur with or after normal anxiety. Let us say that a man is frightened when he is threatened by a gunman. He escapes unharmed, but afterward he begins to have anxiety symptoms. At the time of the incident he has normal anxiety, but instead of resolving it in a reasonable time he continues to be ill and upset emotionally. The continuing symptoms result from repressed sensitivities of the past stored in the unconscious, which break out with or without a recognized provocation in the present environment. This is secondary anxiety.

The symptoms of secondary anxiety are also physical and mental. Physical symptoms usually are those of autonomic dysfunction. They can be imbalances of either the sympathetic nervous system (palpitation, mild dizziness, sweating) or the parasympathetic (muscular aches and pains, functional symptoms involv-

TABLE 2

SECONDARY ANXIETY

Onset:
With or after normal anxiety
From unconscious, without outside stimulus

Symptoms:
Episodic or chronic for years
Physical: autonomic
Mental: fears that are incorrectly selected

Characteristics:
Source: factor from past from unconscious, not completely or correctly identified consciously
In healthy persons: No organic disease
In association with disease: May increase organic pathologic state
Results in poor mental and physical efficiency
No impulsive "fight-flight"
Not group-contagious

Natural course:
Spontaneous remission, progression to chronicity, or development of primal anxiety episode

Treatment:
Insight and understanding of unconscious factor are necessary for cure
Drugs for suppression of symptoms or support

TABLE 3

PRIMAL ANXIETY

Onset:
Occurs with or after normal anxiety, with or after secondary anxiety

Source:
Overwhelming immediate danger; source or solution not completely objectified

Symptoms:
Varying in individual and groups
Mental and physical, with protean manifestations
Acute or gradual disruption of ego
Leads to impulsive "fight-flight," rational or irrational
Spreads by "contagion" to involve groups

Characteristics:
May have "calm before the storm" appearance
"Anything can happen" state. State of acute change. Change often is destructive but can be constructive
May temporarily paralyze rational verbalization
Flight (if possible) usually is chosen over fight

Diagnosis:
"Calm before the storm" appearance often mistaken for normal state
Differentiate when superimposed on normal and secondary anxiety
Physician may feel and correctly identify by "contagion"

Therapy:
Physician must avoid "contagion" by converting his reaction to normal anxiety
Treat group
Treat individual

ing the upper or lower part of the gastrointestinal tract, etc.). The mental symptoms almost always relate to a partly irrational fear of something. It could be a fear of cancer, of height, or of the atom bomb. The symptoms can be episodic, coming in bursts, or they can be chronic, persisting for many years.

In secondary anxiety there always is an unconscious factor, with repressed psychic fixations from the past. Consequently the patient cannot completely or correctly identify the cause spontaneously.

In a person who does not have organic disease, secondary anxiety does not cause organic pathologic change. The symptoms are uncomfortable and a nuisance but they do not cause organic disease. Secondary anxiety occurring in a patient who has organic disease, however, can result in worsening of the organic pathologic state. Thus, a person with a cardiac lesion and coexisting secondary anxiety may have an increase in the organic pathologic involvement.

Unlike normal anxiety, which does not interfere with efficiency, secondary anxiety results in poorer mental and physical performance. Unlike primal anxiety, it does not cause impulsive fight or flight. Patients with secondary anxiety can live and suffer with it as a nuisance and a misery, and the degree of inefficiency varies. It is not "contagious." In this respect, secondary anxiety is strikingly different from primal anxiety.

The natural course of secondary anxiety is either spontaneous remission, progression to chronicity, or development of primal anxiety. Because the main trouble is in the unconscious, insight as to the source is necessary for complete resolution. Dynamic "insight" psychotherapy is therefore the treatment of choice. Drugs may be of some help. Occasionally the patient is able to solve his own difficulty.

Primal Anxiety

Primal anxiety (table 3) can occur in normal persons. It occurs with or after normal

anxiety or secondary anxiety. In short, primal anxiety can occur in anyone.

Symptoms vary in individuals and groups and are so protean that it is impossible to present a repeatable list of symptoms for any individual or group. Generally there are signs of behavioral changes and subtle physical changes. For example, a person who has always slept well may suddenly experience insomnia. Or a person may begin to eat excessively and gain a lot of weight, or suddenly lose weight without reason. All symptoms are manifestations of gradually mounting tension.

In the mental areas, symptoms may be associated with verbal rationalizations of fear, but at times the patient cannot talk directly and spontaneously about it. Even in the face of overwhelming panic he may talk normally. At other times the talk of fear may be almost excessive.

There are signs of acute or gradual disruption of the ego. Primal anxiety leads to increasing mobilization to action. It leads to impulsive fight or flight, either rational or irrational.

One of the complexities of primal anxiety is that it is so basically biologic that all human beings, even normal ones, may be caught up in it. It can spread by "contagion" to involve entire groups. In the Coconut Grove fire in Boston, for example, at first there was normal anxiety related to a recognized threat, but somewhere along the line the group became panicky, and this irrational primal anxiety led to unnecessary self-destruction.

In primal anxiety there is an overwhelming immediate emotion of danger whose source or solution is not obvious. The emotion symbolizes the hurt or death. Thus the emotion itself is something to avoid, destroy or resolve. It is human for each person to attempt to find a source for his anxiety, but frequently the explanation is wrong. Another characteristic of primal anxiety is that many patients live in a state that could be called the "calm before the storm," and this frequently is difficult to identify. However, there are many subtle objective signs and symptoms in other areas that can help one to make a correct diagnosis.

As the patient approaches the time when he can no longer control the gradually mounting tension, there occurs what we call an "anything-can-happen" state, a state of action and acute change. The acute change may involve running away, even suicide—which is, of course, ultimate running away. It may involve murder, which is one form of "fight." It may involve the appearance of acute organic disease. We have observed the occurrence of acute leukemia in three patients who were building up to a primal anxiety. On the favorable side, some of the most dramatic improvements also occur with resolution of this "anything-can-happen" state. Sometimes the change resembles a religious conversion. One patient with ulcerative colitis who had been given up as dying by two internists and a surgeon had a vision in which God told him He was going to help the doctors get him well. The next day the patient had only three bloody bowel movements in contrast to 40 the day before. This is a very dramatic psychobiologic change. We regularly cross our fingers and hope that control and resolution will be possible. There are no advance assurances.

Patients with primal anxiety, and physicians and families too, may be temporarily "paralyzed" verbally and behaviorally and thus may be unable to take appropriate preventive action. For example, consider what happens during a prison riot. The whole group can only disrupt, since they cannot flee. They tear everything apart; they fight. After they calm down, someone asks, "Why didn't anyone suspect this?" And then they all start talking. "Things have been terrible around here for some time. I really have been uncomfortable. The men have been complaining about the food, they have been going to the doctor with vague complaints, and the staff has been taking time off from work." There are many subtle signs, in retrospect. A physician may get calls from half a dozen relatives of a patient, expressing concern about his condition or behavior. Soon you can recognize by these accumulating subtle signs that tension of a very special importance is building up.

Flight, if it is possible, usually is chosen over fight, probably because it does not in-

volve the immediate threat of harm that fight would. A paranoiac person, however, may decide that someone is threatening him and may think, "I am not going to get well until I destroy this person." Then, of course, the situation is different.

The "calm before the storm" in primal anxiety is a most difficult situation to diagnose. The physician often will mistake the state as normalcy, and sometimes this is because he himself needs to avoid this powerful anxiety. Perhaps the most important diagnostic clue is the awareness of primal anxiety in oneself. If the physician handles it correctly, his ego turns it into normal anxiety, signaling danger outside himself. If the physician can master "contagious" primal anxiety, he can "feel" the patient's primal anxiety and know that the calm is deceptive. Also, if he reviews the patient's history and behavior he can recognize the many subtle signs indicating that all is not as good as it appears on the surface. The "calm before the storm" must be distinguished from a normal state. Differentiation from normal or secondary anxiety also must be made. Normal anxiety will resolve in a short time and the source will be correctly identified. Secondary anxiety will continue without causing impulsive fight or flight. When secondary anxiety becomes primal anxiety, something drastic is likely to happen.

Treatment of Primal Anxiety

Almost everyone has experienced primal anxiety at one time or other and reacted to it in one of various ways. If frightened and overwhelmed by it, a person may react so that he would not permit himself to feel the emotion again. On the other hand, if one can integrate and master this uncomfortable emotion, he can utilize it as a useful signal and convert it to normal anxiety. In other words, one's normal anxiety can sense a danger felt by someone else.

If you have never experienced primal anxiety, we would suggest that you walk through the ward of a psychiatric hospital housing the most severely disturbed patients. The chances are that you will feel strangely uncomfortable. You may be feeling the "contagion" of primal anxiety. One can observe it in animals. In dogs, the hair stands on end when they see another animal or a stranger. You may feel the emotion momentarily when a dog jumps on you, when the reaction is added to normal anxiety. But it is often because of the physician's emotional involvement and its evanescence that primal anxiety is the most difficult to study. If the physician cannot feel and recognize it, and if instead he pushes the patient away to protect himself or if he sometimes attacks the patient in anger he may make the situation worse. If a stable ego can recognize what is going on, the control of primal anxiety is almost magic. We are reluctant to use the word "magic" in a scientific paper, but some aspects of psychiatry go back to the days of witchcraft, so perhaps it is not amiss. It is quite remarkable and quite true that a calm leader who *does* see what is going on can stop primal anxiety. It is not essential that an excited patient kill himself. It is not essential that he become psychotic. All of us have heard about a lynching mob which was prevented from "stringing up" someone by a calm person with a rational approach. Awareness of the true state of affairs by a calm and rational physician gives the patient a stable ego with which to identify. Destruction can be prevented.

Once there is awareness that tensions are increasing to a point approaching primal anxiety, the aim of therapy is the stability and the rational understanding of both the individuals involved and the groups around them. The family physician is in a favorable and crucial position to provide the stability and understanding. He sees these situations long before the specialists do. Correct and timely diagnosis can prevent a good deal of misery and unnecessary sickness. It is in this area that a great deal of preventive psychiatry is applicable. We treat both the groups and the individuals. If a whole group is involved, one starts with the more rational members—the healthier ones. Occasionally one will witness panic among a whole group of nurses or an entire family. One has to talk with them, organize what each person is going to do, and keep it rational and appropriate. If there is

TABLE 4

SUMMARY OF NORMAL, SECONDARY AND PRIMAL TYPES OF ANXIETY

	NORMAL	SECONDARY	PRIMAL
Thinking	Reality-oriented, conscious	Neurotic and unconscious	Psychotic-neurotic; primary process
Purpose of anxiety (related to danger)	Signal of danger (known)	Danger unknown, although rationalizations are made	Danger overwhelming. Source known, unknown or misinterpreted
Time	Present; temporary	Present and past; usually lasting	Acute or gradual mounting tension. Brief duration of outburst
Feeling	Painful (+)	Painful (+ to ++++)	"Calm before the storm" or intolerable
Fight-flight (action)	Appropriate	None	Impulsive; rational or irrational. "Anything can happen"
Resolution	Danger removed or avoided	Uncovering of unconscious conflict or suppression with drugs	Removal of threat. Strong leadership. Identification of reality source or solution. Removal of need for impulsive action
Psychic consequences and sequelae	Usually nil	Continued suffering	Improvement or bizarre consequences with psychosis
Somatic tension symptoms	Mild autonomic (+); palpitation, tachycardia, sweating, etc. No sequelae	Autonomic (+ to ++++); annoying or may be damaging if superimposed on organic disease	Mounting tension to point of explosion. Precipitate or resolve psychosomatic illness. Sequelae may be nil, or death may be the consequence. In some instances, dramatic improvement
Contagion (spread to others)	Absent	Absent	Always present
Treatment	None needed as such, although help is normal in some instances	Insight therapy	Prevention possible if condition is recognized before acute disruption

no reality danger, one does have time, so impulsiveness is unnecessary. An episode of primal anxiety involving an entire family could occur when the head of the family has a heart attack, but it does not occur because physicians handle the problem so well. They recognize what is going on, they know what they are going to do. While others may be disturbed, they remain steady. In the navy, many hours are spent planning how to handle acute disruptive situations, because a group of men on a damaged ship have no place to run. *Understanding the reality is enough to keep things steady and avoid the irrational and the unnecessarily destructive.*

Drugs may be used to help control primal anxiety. The physician may call in his colleagues in other fields if necessary. However, recognition of the gradually mounting tension which leads to primal anxiety is the key to prevention and handling of incipient psychiatric emergencies.

Table 4 is a summary of the characteristics of normal, secondary and primal anxiety.

Prolapse of the Uterus and Vagina

LAMAN A. GRAY*

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Childbirth is the most common cause of the various forms of genital prolapse; however, constitutional inadequacy of tissues, postmenopausal atrophy, and intraabdominal pressure also may cause this condition. Treatment may not be necessary in mild, asymptomatic cases. If symptoms are marked and childbearing is desired, repair of cystocele and rectocele, with or without uterine suspension, may be valuable.

If childbearing need not be considered, various operations may be performed. Vaginal hysterectomy, with repair of cystocele and rectocele and obliteration of enterocele, if present, seems to be the most satisfactory procedure.

LAMAN A. GRAY

THE various singular and multiple forms of genital prolapse include prolapse of the uterus, the bladder (cystocele) and the rectum (rectocele) and enterocele. First-degree prolapse indicates that the cervix has dropped partially toward the orifice of the vagina (figure 1). Second-degree prolapse or second-degree descensus means that the cervix is at the level of the outlet of the vagina (figure 2). Third-degree prolapse indicates that the cervix is outside the vagina, to a slight extent or to a marked degree (figure 3). When the uterus is completely outside the introitus, with inversion of the vagina, the condition is called procidentia (figure 4). Sometimes, third-degree prolapse, with only the cervix outside the orifice, has been called procidentia, but the latter term is better reserved for inversion of the vagina or complete prolapse. The posterior hernia of the peritoneum between the cervix and rectum, of slight to severe degree, represents enterocele, which is not uncommon.

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Causes

The most common cause of prolapse is childbirth; however, in some cases it is congenital, apparently developing from a nerve and muscle weakness which becomes evident

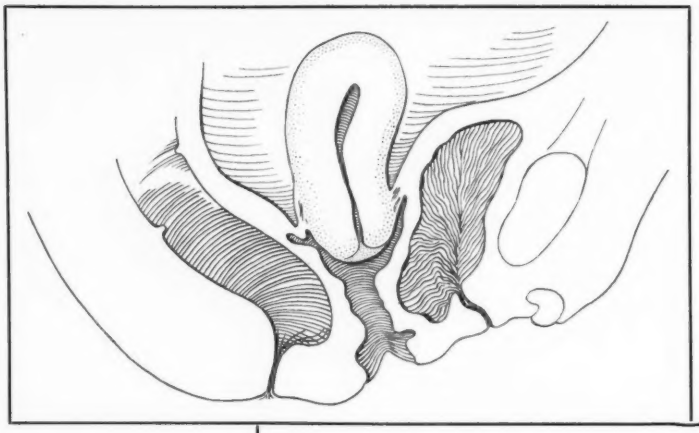

FIGURE 1. First-degree prolapse.

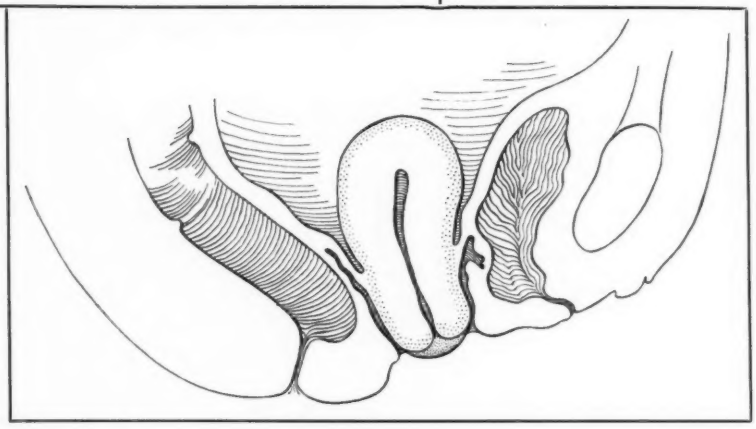

FIGURE 2. Second-degree prolapse.

in later life. The birth of the fetus at term stretches the diameter of the cervix 10 or 12 cm. or more, and in the process of bearing down, with the expulsive, contracting forces of the uterus, the supporting cardinal ligaments and uterosacral ligaments are greatly overextended. As the fetal head and shoulders pass through the vagina, the levator muscles, the urogenital diaphragm, the various fasciae and the smaller muscles are stretched markedly to allow the fetus to come through the outlet. In the majority of young women, a remarkable contraction after delivery returns these structures almost to normal, and the elasticity of the muscles and ligaments may cause a regression to their previous state. As the years pass, the original stretching at the time of delivery may gradually return and allow degrees of prolapse of the uterus, as a rule associated with cystocele and rectocele, and at times with enterocele. After multiple deliveries, the degree of prolapse often is more severe, but this is not always true. Occasionally, a woman may have been delivered of many children and yet have relatively little prolapse and relaxation, whereas a patient who has given birth to only one child may have severe degrees of cystocele, rectocele and advanced prolapse.

Prolonged labor and difficult delivery may well be factors in the development of prolapse, although this is not always true. The pelvic floor is far better preserved in the large percentage of women who have a properly performed episiotomy, and its accurate repair immediately after delivery, than in those who have delivery without episiotomy. That the episiotomy and repair may prevent the development of prolapse of the uterus is not clear,

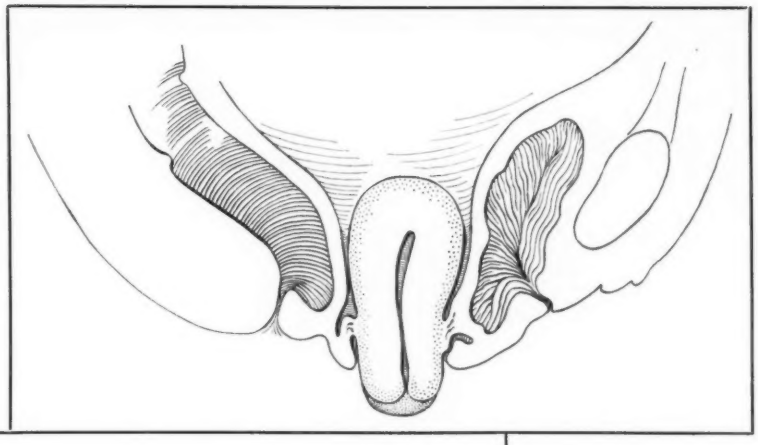

FIGURE 3. Third-degree prolapse.

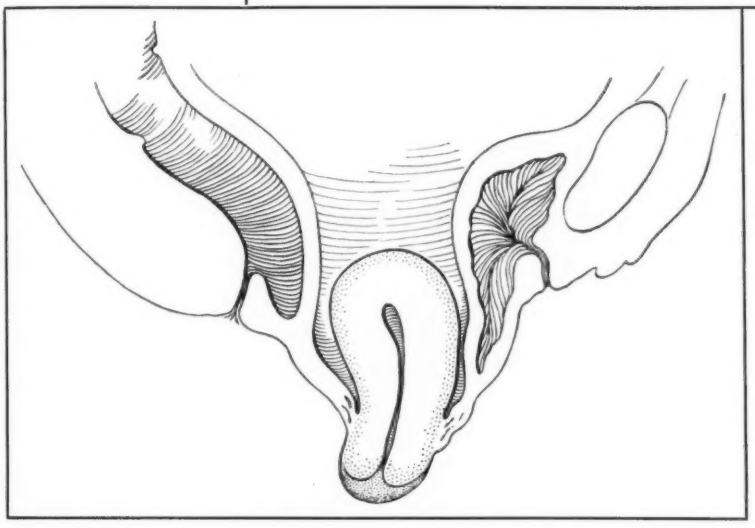

FIGURE 4. Procidentia.

but perhaps the outlet muscles are important in descensus of the uterus.

Occasionally, degrees of prolapse of the uterus, cystocele, rectocele and enterocele occur in nulliparous women. At times the uterus prolapses outside the vagina. Obviously, overstretching of ligaments could not cause this descensus; evidently, there must have been an unusual degree of weakness in the supporting muscles and ligaments. X-ray films of the spine in these cases frequently reveal the occult spina bifida, which apparently has some association and probably indicates a nerve weakness that may be responsible for the loss of tone in the muscles and ligaments and allows prolapse to occur. The discovery of occult spina bifida remains a curiosity, because surgical repair is the only real treatment, although recurrence of the prolapse may follow.

Lennon[1] stated that prolapse of the uterus may be caused by (1) constitutional inadequacy of the tissues, (2) atrophy occurring after the menopause, (3) birth trauma, or (4) increased intraabdominal pressure. He pointed out that prolapse may be prevented by (1) avoidance of a prolonged second stage of labor, (2) avoidance of forceps before complete dilatation of the cervix, (3) avoidance of precipitate and breech deliveries, (4) performance of episiotomy routinely, and (5) use

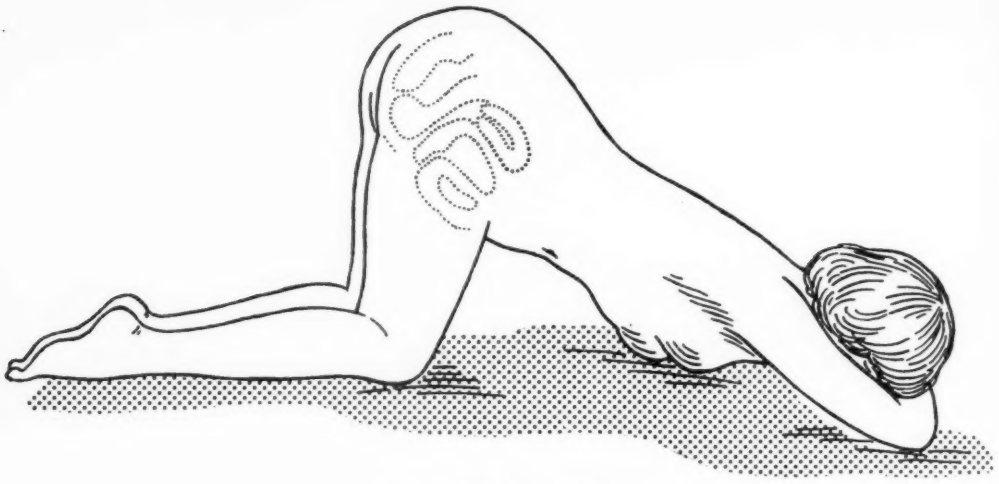

FIGURE 5. Knee-chest position.

of postnatal exercises of the outlet and levator muscles. I am inclined to believe that birth trauma and subsequent loss of muscle tone in later years account for prolapse of the uterus in 95 per cent of cases.

Symptoms

The symptoms of prolapse are primarily bearing down and pressure sensation deep in the pelvis and a feeling that the inside of the abdomen will fall out through the orifice, associated with degrees of quite low backache. Often, dyspareunia and disturbances of menstrual functions may be present. These symptoms may be mild or severe and disabling. Marked prolapse may produce no symptoms in some women, while mild prolapse may cause symptoms in others.

Diagnosis

The diagnosis of prolapse often is made by the patient herself, who states that the neck of the womb or bladder has dropped to the outlet or outside the vagina, because she has felt it and has seen it with a mirror. The conclusive diagnosis is made by gynecologic examination, in which the cervix is seen at the outlet of the vagina or outside the vagina or the vulva (in second-degree and third-degree prolapse). With first-degree prolapse, one notes when the patient strains that the cervix, usually with the bladder and rectum, bulges down into the vagina in varying degrees.

When there is apparent prolapse or complaint of the previously mentioned symptoms, a tenaculum may be used to draw down the cervix gently or moderately to determine the degree of descensus. Also, at the conclusion of the pelvic examination, the patient may well be examined in the standing position with her legs somewhat apart. The examiner places two fingers in the vagina to feel the bulging of the vaginal walls and the descent of the cervix on straining. It is in this position that most of the symptoms occur that are related to prolapse, and it is helpful in evaluating a case to palpate the vagina and cervix with the patient in the erect position.

Treatment

Exercises—The treatment of genital prolapse generally depends on the symptoms associated with it. If there are no symptoms in first-degree or second-degree prolapse, with related cystocele and rectocele, then no treatment is advised. If the symptoms of bearing down and pressure are relatively mild, the knee-chest position (figure 5) may help circulation; restore the normal position of the uterus, at least for a short period; and be

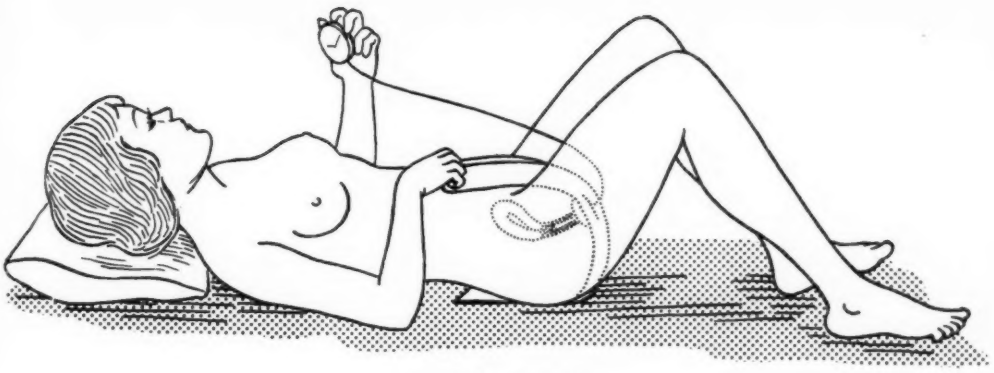

FIGURE 6. Kegel exercise.

sufficient to relieve symptoms. The Kegel exercise (figure 6) of constriction of the levator and vaginal muscles, the so-called pubococcygeal muscles, may aid not only stress incontinence but also prolapse to some extent.

Pessaries—Young women in the childbearing age should be allowed to maintain their fertility because they may desire to have more children. Particularly for young women who may desire more children, the Smith or Hodge pessary may be inserted, to be changed at intervals of six or eight weeks; the vagina should be observed for ulceration and irritation. The pessary may give complete symptomatic relief of the minor degrees of prolapse. Similarly, in elderly women who are not good surgical risks or who fear surgical procedures intensely, pessaries may be inserted and changed at regular intervals. While the Smith and Hodge pessaries may be satisfactory, the large ring pessary or the doughnut pessary, which is soft and rubbery and contains air in its center, may be used; however, the soft rubber is more irritating than plastic materials. In the elderly patient the Gellhorn pessary (figure 7) is preferred, as it gives a more satisfactory result in supporting the cervix. The use of pessaries depends on a reasonably satisfactory perineal outlet support. If the perineal outlet has no support, the pessary cannot be maintained in place satisfactorily. Use of the pessary may be continued as long as desired in the young patient, and as long as necessary in the elderly patient who has medical complications or who fears an operation. Mechanical vaginitis, and even severe ulceration, may be produced by the pressure of pessaries on the wall of the vagina. Granulation tissue also frequently results. If forgotten and left in the vagina for prolonged periods, the pessary may become embedded in the vaginal mucosa; it then can be removed only by surgical excision through the vagina.

Operative procedures—If the symptoms are marked, surgical operation is the preferable treatment in both young and old patients. An exception is the young patient who wishes more children in the immediate future; she may receive the temporary benefit of pessaries

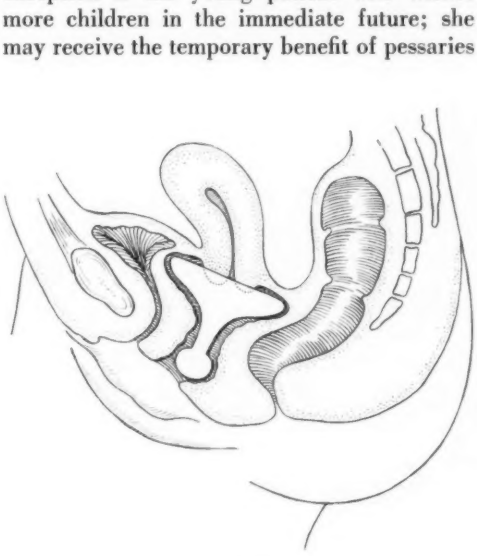

FIGURE 7. Gellhorn pessary.

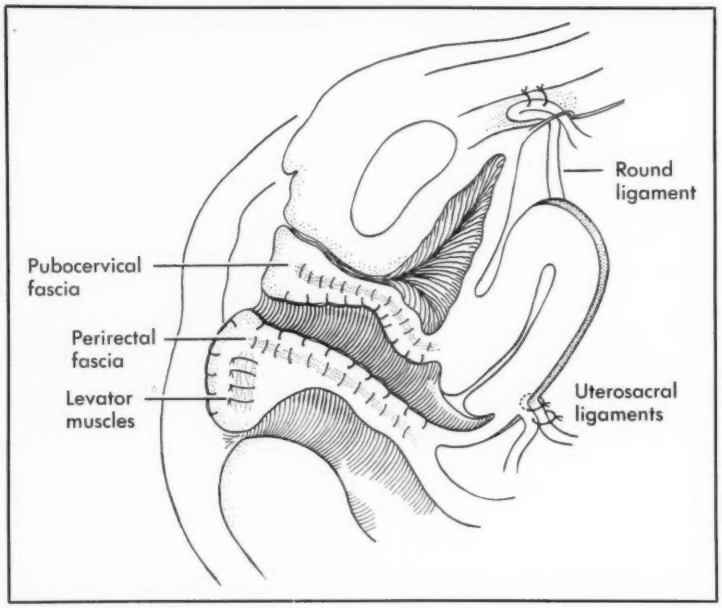

FIGURE 8. Anteroposterior repairs and suspension.

and be encouraged to complete her family. Operation is not indicated if the symptoms are minor.

Six basic operative procedures may be used in treating prolapse of the uterus. A conservative intervention is advocated for the young woman who has marked symptoms from prolapse, cystocele and rectocele and who has not completed her family, but does not wish to have more children in the next few years. This procedure involves repair of the cystocele and rectocele. In some instances, when there is prolapse of the cervix, this may be followed by abdominal suspension of the uterus and shortening of the uterosacral ligaments in order to draw the cervix back into the pelvic cavity (figure 8). With subsequent pregnancy, there may be recurrence of cystocele, rectocele and prolapse or retroversion, but this is a matter of no more concern than in the normal nulliparous patient who desires to have a child. The relaxations, displacements and prolapses that occur in the normal patient are not deterrents to pregnancy and delivery. As a rule, cesarean section is not necessary; however, this is a matter for individual decision.

Another procedure used for prolapse is the Fothergill operation (figure 9). Repair of the cystocele and rectocele is performed, along with amputation of the cervix and suturing of the cervical ligaments in front of the cervix. The latter procedure is to act as a deterrent to subsequent prolapse by displacing the cervix posteriorly. However, there are degrees of recurrence after this procedure, and all of the varying diseases of the uterus, particularly those caused by enlargement and heaviness, may appear in subsequent years. It appears that sterility is increased after this operation. Recent studies on incompetence of the cervical os causing late miscarriage, due to disruption or loss of the sphincter in the cervix, may be applicable to the uterus involved in the Fothergill operation. This operation has been used for 70 years in Great Britain as the chief treatment for prolapse. It was first performed by Duncan of Manchester in 1879; however, the situation in England has changed materially in the past few years, and vaginal hysterectomy is being accepted more widely now.

Solomans[2] in 1955 reported on 190 Fothergill operations, but only 62 patients were followed. There were recurrent small cystoceles in 24, moderate cystoceles in 10, and

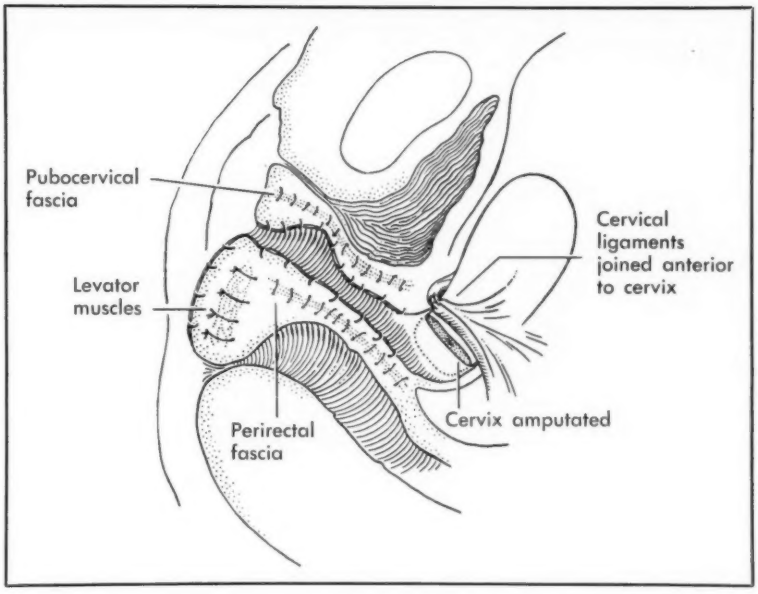

FIGURE 9. Fothergill (Manchester) operation.

small rectoceles in eight. Three patients had a deficient perineum, and one patient had an eroded cervix. Solomans postulated that the retained uterus may have some value in itself. Gordon and Gordon[3] in 1957 reported on 380 Fothergill operations. Prolapse of the uterus was cured in every case. There were four recurrent cystoceles, six patients with stress incontinence, and four recurrent enteroceles. It is not clear that more than two patients became pregnant. This report is enthusiastic.

The Watkins interposition operation (figure 10) is a procedure in which the corpus of the uterus is drawn beneath the bladder and sutured into the vaginal wall. The cervix, as a rule, must be excised in order for the uterus to be displaced in this position. Posterior colporrhaphy follows. This method has the same disadvantages as found in the Fothergill operation, except that a greater problem exists with the latter in the possible necessary excision of the uterus at a later date. The scar tissue and adhesions between the bladder and vagina may make subsequent excision of the uterus for pathologic lesions most difficult. Pregnancy obviously is impossible, and tubal ligation must be performed in the patient before the menopause. This operation has lost most of its popularity in the last 20 years. However, Brady[4] in 1953 reported a high degree of success in operative procedures of this type. T. S. Cullen was a strong supporter of this operation and taught me this technic; however, we have not used it for the past 20 years.

In the Spaulding-Richardson operation (figure 11), the corpus of the uterus and the cervix are separately excised through the vaginal approach, and the body of the cervix is used as a keystone into which the cystocele repair may be anchored. This procedure may be difficult, in fact, more difficult than total removal of the uterus through the vagina. Subsequent abnormalities in the small stump, such as irregular bleeding, discourage many from using this otherwise valuable procedure. However, this method has its proponents. TeLinde[5] reported on 400 such operations; one patient had recurrent cystocele and five had prolapse of the vaginal vault. Mast[6] reported good results in 52 cases. He removed the corpus before the cervix and cored out the stump. A generous percentage of the patients had scanty menstruation, and one had menorrhagia. In my opinion, while the keystone principle had its advantages, the scant or irregular bleeding during the postoperative

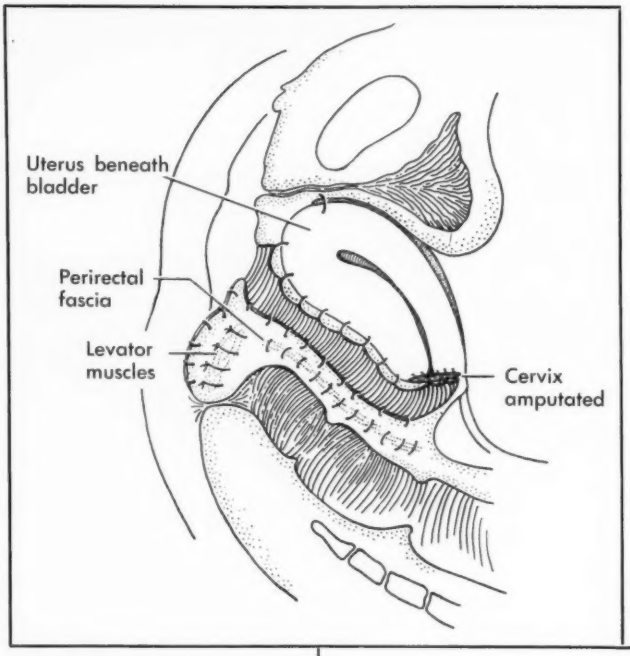

FIGURE 10. Watkins interposition operation.

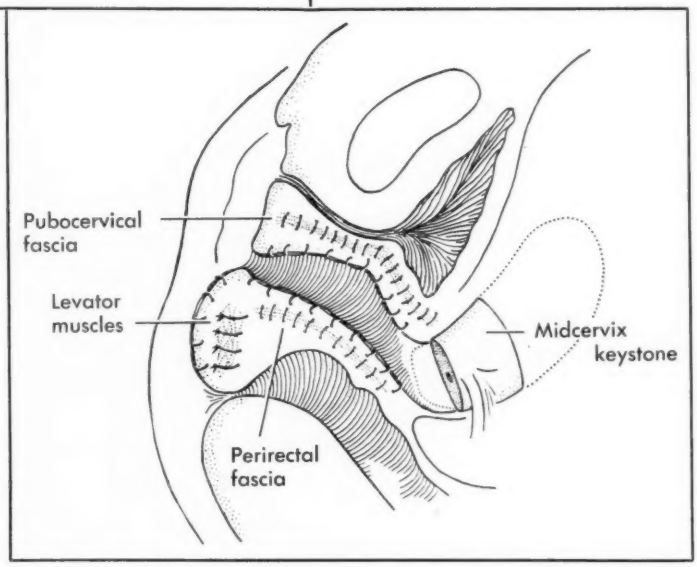

FIGURE 11. Spaulding-Richardson operation.

years makes this an undesirable operation.

In the Le Fort operation a portion of the vaginal mucosa is removed from anterior and posterior walls of the vagina and the denuded areas are sutured together. Le Fort in 1879 thought this was a logical procedure because he had never seen prolapse in a patient with septate vagina. While this procedure has been used on occasion, it has never appealed to me.

The most popular treatment for prolapse today is that of vaginal hysterectomy with repair of cystocele and rectocele[7] (figure 12).

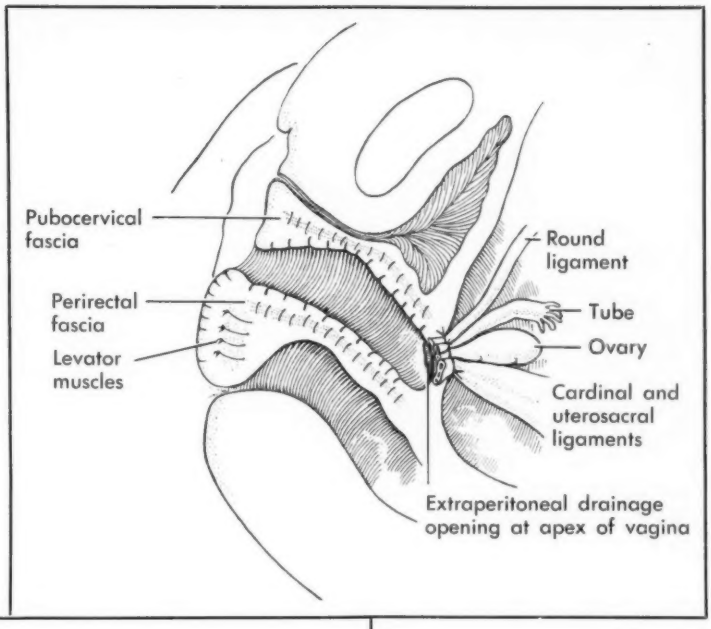

FIGURE 12. Vaginal hysterectomy with repair of cystocele and rectocele.

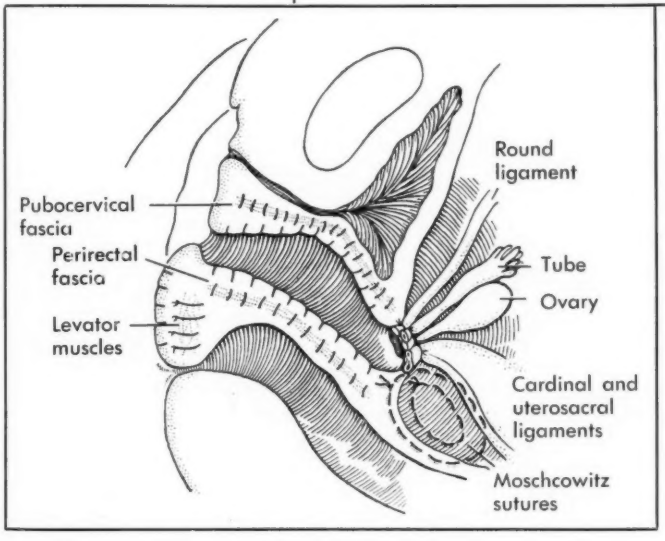

FIGURE 13. Vaginal hysterectomy with abdominal Moschcowitz sutures.

Illustrations were furnished by courtesy of the Department of Visual Education, University of Louisville School of Medicine, Louisville, Kentucky.

Numerous variations of this operation have been advocated for the treatment of prolapse, especially in third-degree prolapse and procidentia. While some have drawn the ligaments together in the midline or have placed them beneath the bladder as a sling and sutured them into the arc of the symphysis, probably most surgeons perform a conventional vaginal hysterectomy and attach the ligaments in the angles. Then repair of the cystocele and rectocele is performed. Recurring cystocele is annoying to the surgeon, although it is more often asymptomatic to the patient. In 376 consecutive vaginal hysterectomies which we performed, there were 23 small or moderate recurrent cystoceles. This condition develops

in the first place because the fasciae and muscles beneath the bladder are not strong enough to retain this organ at its desired level. Recurrence is expected in a certain percentage of cases because of the weakened character of the tissues. Recurrence of a rectocele also may follow its repair, but this is uncommon.

The occurrence of an enterocele must be suspected in all patients with prolapse and a rectocele. In fact, if the rectocele alone is to be repaired, one always must search for a peritoneal sac at the apex of the posterior vaginal wall. If found, it must be ligated and excised, and the fasciae and muscles must be drawn across in front of it in the repair. In the course of vaginal hysterectomy, any indentation of the peritoneum below the vaginal cuff always must be excised, and any true enterocele sac must be thoroughly removed and the cul-de-sac carefully closed in the midline.

We found 36 enteroceles, some small, in 376 cases of vaginal hysterectomy. Suturing the uterosacral ligaments in the midline has been advised. McCall has treated the enterocele by closing the cul-de-sac with three purse-string sutures and has sutured the posterior vaginal wall into the cul-de-sac to deepen the vagina. The latter vaginal sutures aid in maintaining depth to some extent. Shortening is the rule with any extensive repair of an enterocele. The recurrent enterocele after vaginal hysterectomy probably appears in at least 3 per cent of patients over a long period, and perhaps in a larger number. Six enteroceles recurred in the 376 vaginal hysterectomies we performed. Possibly the number of recurrent enteroceles may be decreased if the sacs are searched for and obliterated in the original operations.

With the large enterocele and prolapse, one may perform the vaginal hysterectomy, repair of the cystocele and rectocele, excision of the enterocele sac, and then the abdominal operation of obliteration of the cul-de-sac by the Moschcowitz procedure (figure 13). This has been advocated recently, particularly by Bennett, and is a valuable procedure. In six cases we have had good results in performing this abdominal procedure with vaginal hysterectomy. When postoperative complete prolapse and inversion of the vagina occur, repeated repair of the cystocele and rectocele and the abdominal Moschcowitz sutures may prove curative. Various strap operations have been advised for treating posthysterectomy prolapse of the vagina in which strips of the abdominal wall fasciae are drawn down and attached to the vagina; however, these procedures are much more complicated and difficult to do.

At times, the elderly patient who has procidentia and complete inversion of the vagina, with the uterus completely outside the vagina, may be treated by vaginal hysterectomy and total vaginectomy, with high ligation of the peritoneal sac; this is followed by sutures beneath the bladder and over the rectum to support these organs and by closure of the dead space in-between. We have had excellent results with this procedure in five elderly patients. Svesko[8] had good results in treating one patient with irreducible procidentia by vaginal hysterectomy and total colpectomy.

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Management of the Child With Nasal Allergy

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A correct anatomic and etiologic diagnosis should be made before therapy is begun in children with allergic rhinitis. A proper investigation includes a carefully taken history and well-chosen skin tests.

Management is planned according to the individual case. Symptomatic treatment often is necessary until environmental control has been established. Hyposensitization should be reserved until found necessary. Only when other measures are not successful should antihistamines be used on a long-term basis.

Both the patient and his parents should be educated in the underlying principles of management.

GEORGE B. LOGAN

In a day when the world is faced with atomic bombs, space travel and fouled-up international relations, this paper presents what may be considered as a rather small subject. The management of the child who has nasal allergy is a small medical problem only in that it occurs in a child, and many people think that all problems in children are small.

This problem concerns the child who has a runny, stuffy, itchy, uncomfortable nose. It is so easy when one hears by telephone or in the office about such a child to prescribe nose drops, an antibiotic syrup, perhaps an antihistaminic agent, or an injection of penicillin. The physician may wish to utilize all these means of treatment if the patient has been to the office three or four times within a short period. Some physicians sincerely hope that they will not see him again because they apparently have so little to offer in the way of

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TABLE 1

CAUSES OF NASAL OBSTRUCTION IN CHILDREN

FOREIGN BODIES
ANATOMIC VARIANTS
Adenoid hypertrophy
Choanal occlusion
Deviated septum
NEOPLASMS
Sarcoma
Polyps
INJURY
Direct trauma
Reaction to inhalation of fumes
ALLERGY
Perennial allergic rhinitis
Recurrent upper respiratory infections
Seasonal hay fever or pollenosis
INFECTIONS
Common cold
Purulent rhinitis
Adenoiditis
Sinusitis
Diphtheria

therapy. However, many things can and should be done for such children.

Differential Diagnosis of Nasal Obstruction

Before anything can be offered therapeutically, the diagnosis must be made. Table 1 lists most of the causes of nasal obstruction in children. The common cold is the most frequent cause of nasal obstruction. A foreign body in the nose is not uncommon in a child. Physicians in rural regions occasionally see a child who has pushed a bit of corn or other seed up into a nostril, often into a rather inaccessible site. It then swells and produces inflammation; as a result, the offending agent can be seen only with difficulty. Children from cities are no less likely to insert any of a variety of objects into the nose. A father once excitedly brought in a child for an "emergency adenoidectomy," stating that the adenoids were hanging out of the nose. Examination disclosed the red eraser of a lead pencil protruding from the nostril.

One of the most common causes of posterior nasal obstruction is enlarged adenoids. I believe that most children less than three years of age who have enlarged adenoid tissue either are allergic or come from an allergic family. Frequently, the large adenoids must be removed surgically to open the airway. This procedure will be of only temporary value unless treatment of the allergic state is instituted concomitantly. Regrowth of adenoid tissue frequently is noted in allergic children. Large adenoids in some young children and in many older ones may be on the basis of chronic infection. Removal of the adenoids is necessary to eliminate infected tissue and allow adequate drainage.

Choanal occlusion is an anomaly that causes symptoms of obstruction first during the neonatal period; its presence should be suspected in any newborn having trouble in breathing through the nose. It is confirmed by finding that a small catheter cannot be passed through the nose into the pharynx.

It is easy to see a deviated septum if the nose is carefully examined. Usually, this condition is best left untreated until the child's face is fully developed, which ordinarily occurs at the age of 14 to 16 years. Occasionally, however, operative correction must be done earlier if severe obstruction is present.

Neoplasms occur rarely, but when they do they are likely to be extremely malignant. One of our young patients had a large mass in his nose that was easily seen. It was so friable and vascular that direct biopsy was avoided; instead, one of his enlarged cervical lymph nodes was biopsied. Histologic study showed an extremely malignant neoplasm. Roentgen therapy was given to the nasal lesion and the cervical metastatic tumors, with excellent immediate results. The boy subsequently died of distant metastasis.

Polyps are nonmalignant neoplasms. They are most commonly a complication of allergic disease, but infections also may produce them. Polyps have been observed in some children with fibrocystic disease.

Direct injuries to the nose and reactions to fumes may cause nasal obstruction. It usually is not difficult to discover such a cause.

One other reaction, which may be properly termed an iatrogenic situation, is the condi-

tion referred to as "vasomotor rhinitis medicamentosus."[1] This is simply the reaction of the nasal mucous membrane to the overzealous use of nose drops.

In addition to the aforementioned common cold, the bacterial complications of a cold, namely, rhinitis, adenoiditis and sinusitis, are common causes of nasal obstruction.

Finally, I would call attention to diphtheria. This disease still occurs sporadically or in epidemics in regions where immunization has been neglected. A total of 836 cases was reported in the United States during 1959.

Two other infrequently encountered conditions that might be added to this etiologic list are Kartagener's syndrome (dextrocardia associated with bronchiectasis and sinusitis) and hypothyroidism.

Clinical Aspects of Nasal Problems Related to Allergy

I have borrowed two terms from Glaser,[2] namely, "perennial allergic rhinitis (PAR)" and "recurrent upper respiratory tract infection (RURI)." The former refers to allergic nasal difficulty that occurs all year. The latter refers to intermittent "colds" that sometimes are considered to be caused by infections; in between episodes, the child appears to be free or nearly free of nasal disease. The term "vasomotor rhinitis" often is used to designate these syndromes. However, factors other than an allergic reaction may produce a vasomotor reaction in the nose. Hence, all allergic rhinitis is vasomotor, but not all vasomotor rhinitis is allergic. The terms "hay fever" and "pollenosis" refer to seasonal allergic rhinitis.

The mucous membrane of the nose at the beginning of an allergic reaction is moderately swollen and red. With thin serous to mucoid discharge, the picture closely resembles that seen early in an infection of the respiratory tract. As the condition becomes more subacute or chronic, the membranes appear more pale than red, at times being "boggy." Infants may show this procession of events, although the nasal mucous membrane in some normal infants at times is paler than that of an older child. The adenoid tissue also swells in a youngster with allergic rhinitis.

TABLE 2

IMPORTANT ETIOLOGIC FACTORS IN ALLERGIC NASAL DISEASE IN CHILDREN

INHALANTS	
Seasonal	
Pollens, molds	
Nonseasonal	
Home:	house dust, allergens in father's occupation, animal hair
School:	chalk dust, etc.
INFECTIONS	
Respiratory tract infections	
INGESTA	
Foods, drugs, gums	
INJECTIONS*	
Serums, antibiotics, vaccines, biologic preparations	
PSYCHOGENIC FACTORS†	
Various emotional reactions	
PRECIPITANTS	
Variations in temperature or humidity	

*This group is not discussed in the text.

†Cases caused by these factors have been rare in my experience.

One occasionally encounters a child who has either complete or nearly complete posterior nasal obstruction from a condition other than allergic disease. The mucous membranes of such a child appear pale and a little shiny.

Etiologic considerations—If one makes a clinical diagnosis of allergic rhinitis, the next step is to make an etiologic diagnosis. Table 2 lists in order of importance those general classes of agents that are usually responsible.

Inhalants—The seasonal factors often can be sorted out by history. However, it is often difficult to distinguish accurately between patients who are sensitive to molds and those sensitive to ragweed. The history always should be checked by skin testing. The nonseasonal factors in the home or on the farm sometimes can be identified on the basis of history, but one usually requires the help of skin testing as well.

The school environment may be important. Some of the elements encountered there may be irritating rather than allergenic. One of these is chalk dust, exposure to which may aggravate allergic rhinitis or asthma. A 10

year old boy had both asthma and allergic rhinitis. After these had been well controlled for many months, he began to have recurrence of rhinitis and asthma each week end. Investigation disclosed that the teacher had evolved a new scheme for rewarding the children who were good; they were allowed to clean the erasers on Friday afternoon.

Infections—Infection is an important etiologic agent. Its effects are exerted more as a precipitating factor than as bacterial allergy of the immediate type. However, a delayed type of hypersensitivity undoubtedly may occur as a result of bacterial infection. This delayed reaction does not cause allergic rhinitis. Nasal mucous membranes in allergic children often appear to be more readily infected than do those in normal children.

Ingesta—Ingestive factors are not the important etiologic agents in children that they formerly were considered to be. Skin testing in my experience has not been very helpful in establishing a correct diagnosis of food allergy. The use of an elimination diet is the best form of study. The etiologic role of one or more foods sometimes is obvious. Unless this is so, one should be sure that the possible role of inhalant and infectious agents has been thoroughly investigated before any dietary trials are made.

Occasionally, one stumbles onto the causative food by serendipity. A 14 year old girl was brought for consultation because of obesity. It was evident that the patient also had mild chronic rhinitis, presumably on an allergic basis. The parents asked that we not investigate the nasal problem but help them only with reduction of weight. After dietary treatment for six weeks, the patient had lost both the required amount of weight and the runny nose. It was found subsequently that the chocolate that had been eliminated from her diet was responsible for her nasal condition.

Psychogenic factors—Emotional reactions can cause changes in the nasal mucous membranes similar to those produced by allergens.[3] This is a vasomotor rhinitis but not a truly allergic type.

Precipitants—Precipitating factors, particularly sudden changes in temperature and humidity, may cause nasal symptoms in normal children or make worse the nasal symptoms in those having allergic disease. Persons who consider themselves to have normal nasal mucous membranes are accustomed to accepting the changes in the nose that occur when they go from an air-conditioned room into warmer and more humid areas or, in winter, from heated interiors to the cold outside air. Such irritating exposures usually cause worsening of allergic rhinitis.

TABLE 3

SUGGESTED MINIMAL NUMBER OF ANTIGENS FOR SKIN TESTS IN CHILDREN WITH NONSEASONAL ALLERGIC NASAL DISEASE

Cat hair	Mixed feathers	Silk
Cattle hair	House dust	Tobacco
Dog hair	Kapok	*Hormodendrum*
Goat hair	Orrisroot	*Alternaria*
Hog hair	Pyrethrum	Bermuda grass
Horsehair	Cottonseed	Timothy grass
Rabbit hair	Flaxseed	Ragweed (giant or small)
Sheep's wool	Karaya gum	

Diagnostic considerations—A proper investigation of allergic disease includes not only a well-taken history but well-chosen skin tests as well. The antigens for skin tests listed in table 3 are often adequate. It is not necessary to do 300 skin tests in each patient to settle the cause of every allergic disease. Sometimes, none of these tests are needed, but skin testing usually is helpful. However, the results are not infallible and must be properly interpreted. When skin tests are done on children less than five years of age, one must be careful about ruling out potential etiologic agents that give negative reactions. Many such youngsters have negative skin reactions to agents that produce clinical allergy in them. If direct contact between a patient and an agent, such as a dog, always causes allergic rhinitis, a skin test is not required. The family should be advised to get rid of the dog. This is usually a task that is easy to suggest but difficult for the family to carry out.

Study of smears of nasal secretions for excessive numbers of eosinophils sometimes is helpful when it is questionable whether the nasal secretion of a given patient is caused by

an allergic reaction. It need not be done routinely.

Consultation with an otorhinolaryngologist who is interested in children is often a fruitful means of investigation. The otorhinolaryngologist should look particularly for evidence of infection or polyps.

Sinus disease caused by bacterial infection does occur in children. Those having allergic disease often have clouding of one or more of the sinuses on roentgenographic examination; this may be caused by swollen mucous membranes and need not be evidence of sinus infection.

Complications—The complications of allergic rhinitis may be noted in the nose, ears or lungs. In the nose, one of the two chief complications is the development of polyps; these occur chiefly in children who have perennial allergic rhinitis rather than the seasonal variety. If the polyps are large and obstructive, they should be removed surgically. Otherwise, the management should be medical. These lesions regress when proper measures for environmental control are instituted or when hyposensitization is added. The use of steroids will shrink polyps, but the effect is only control, not cure.

The second nasal complication is infection. This may be purulent rhinitis or sinusitis, the former being more common. As long as poor drainage is present, it will be difficult to eradicate the infection. Efforts to induce better drainage often may be more successful than is the use of antibiotics in eliminating the infection. In my experience, I have seen an unusually high percentage of positive cultures for *Hemophilus influenzae* in the nasopharynx of allergic patients. This must be considered in choosing an antibiotic drug for treatment.

Aural complications are chiefly loss of hearing, secretory otitis, and purulent otitis media. Loss of hearing is the result of blockage of the eustachian tube, usually by swelling of lymphatic tissue or the mucous membrane around the nasopharyngeal ostiums. Secretory otitis may be caused by obstruction of the eustachian tube from uninfected secretion or by incompletely resolved or insufficiently treated purulent otitis media. In treating these complications, one usually needs the help of an otorhinolaryngologist. The basic need, however, is to institute proper antiallergic measures.

Consideration of the pulmonary complications of asthma is beyond the scope of this discussion.

Treatment

After a clinical and etiologic diagnosis of allergic rhinitis has been established, one must start treatment. It is as helpful for these patients and their parents to understand some of the principles of treatment and the basis of allergic disease as it is to have diabetic patients instructed in these aspects of diabetes.

Environmental control—Environmental control is not easy; however, it is practical. A dust-sensitive child who has allergic rhinitis often is relieved almost completely by having the parents make the bedroom and the television area as free from dust as possible. The success of this dustproofing effort is usually in direct proportion to the adequacy of instruction and the enthusiasm of the instructor.

Hyposensitization—Hyposensitization is often necessary. It is indicated more often in the treatment of seasonal allergic rhinitis than it is in the perennial form. The diagnosis of the seasonal disease should be established by at least two seasons of rhinitis substantiated by skin testing before the series of injections is undertaken. However, the occurrence of one season of severe rhinitis or the presence of asthma in association with the rhinitis is reason to advise hyposensitization.

I strongly urge that measures for environmental control in children with perennial allergic rhinitis should be meticulously carried out before hyposensitization is instituted. If these forms of treatment are used concomitantly, hyposensitization may be given the credit for improvement that rightfully has been brought about by environmental control.

Symptomatic therapy—Symptomatic treatment often must be used until environmental control is completely established. It is often adequate for mild seasonal disease. However, it is rarely wise to use it on a long-term basis, and fairly good to good symptomatic control

should not be the sole goal of the treatment.

Antihistamines—The various antihistaminic agents are extremely helpful if the dose is adequate and the time intervals between doses are properly established. There is no hard and fast rule about dosage. In general, drugs of which 50 mg. is the average single dose for an adult are given to children in a dosage of 2 mg. per pound of body weight per 24 hours; this total amount usually is divided into four or five daily doses. Drugs of which 25 mg. is a single dose for adults are given in amounts totaling 1 mg. per pound per 24 hours divided into four or five doses. Those of which 4 mg. is the single dose for an adult may be given in dosages of 2 mg. two or three times daily to a two year old child, and four times daily to a six year old child; a 10 year old patient often requires 4 mg. of such a drug two or three times daily. Long-acting preparations may be administered in place of the regular drugs after an adequate dosage for the individual child has been determined. No particular antihistamine is best; the best is the one that works best for the patient.

When the problem of allergy is acute, one or two days of treatment with an antihistamine will be an adequate time in which to decide its effectiveness. The drug may have to be given for one or two weeks to a child with a chronic problem before a good effect is evident. A combination of ephedrine and an antihistamine sometimes gives better results than does either drug alone.

Steroids—Steroids are seldom necessary in treating children who have nasal allergy. These agents can be used systemically or locally in children with unusually severe hay fever that does not respond to other measures, but they are given only as a "bailing-out" procedure.

Comment and Conclusions

The management of children who have allergic rhinitis should be based on a correct anatomic and etiologic diagnosis. The parents and the child must be educated in the principles underlying the management of allergy. Meticulous environmental control is necessary when indicated. Dustproofing a bedroom does little good unless it is done well; dustproofing the bedroom but having the child spend an hour a day in a dusty area watching television is poor environmental control. Half-hearted instructions will give half-hearted results.

Hyposensitization should be reserved until it is found to be necessary. If it is necessary, consultation with an allergist is usually wise.

Symptomatic treatment must be given, but the physician and the family should not look to good symptomatic results as the only goal of treatment. The use of an antihistaminic agent in full dosage often brings relief. However, only when other measures have been tried unsuccessfully is one justified in using these drugs on a long-term basis. The administration of steroids is seldom necessary in treating children with nasal allergy.

Infections must be treated specifically when encountered, and drainage must be established.

To be most effective, the entire program of management must be tailored to fit the individual child.

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Diabetic Neuropathy

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There are many kinds of diabetic neuropathy. Involvement may occur in the cranial or peripheral nerves or the autonomic nervous system, and is more frequently seen in the lower extremities than in the upper extremities.

Arteriosclerosis and vitamin-dietary deficiencies are known causes of neuropathy. Unknown intermediary metabolites also may be implicated.

General treatment includes skin care and relief of pain. More specific treatment is determined by the type of neuropathy.

KENDRICK SMITH

DIABETIC neuropathy occurs in a variety of forms. Depending on the interest of the physician and the care with which the patient is examined and questioned, an incidence of from less than 5 per cent to over 50 per cent has been reported (table 1). Our experience with some 1200 diabetic patients hospitalized yearly has been used to evaluate the significance of diabetic neuropathy to the patient. Five to 24 per cent of our hospital patients have diabetic neuropathy as one of the major complaints on admission. This incidence, too, varies with the care used in taking the history.

Types of Diabetic Neuropathy

Functional or hyperglycemic neuritis occurs either early in diabetes or during episodes of hyperglycemia and acidosis. It consists chiefly of cramps, muscle aching and tenderness, fatigue, numbness, and burning and heat of the skin, especially of the lower extremities. Its chief characteristic is probably the rapidity with which these complaints are relieved by control of the hyperglycemic status.

In this same general classification should be included the post-treatment or so-called insulin neuritis, which occurs one to three

TABLE 1

REPORTED INCIDENCE OF DIABETIC NEUROPATHY

INCIDENCE (PER CENT)	INVESTIGATORS
<5	Lande and Pollack; Joslin, Murphy and Moxon; Fein, Ralli and Jolliffe; Rundles
5-50	Broch and Klövstad; Bonkalo, Barach and Smith's group
>50	Goodman et al.; Jordan et al.; Collens et al.

weeks after the beginning of antihyperglycemic therapy and which can be expected to disappear as treatment is continued. This condition should not be confused with the paresthesia, muscle imbalance and ataxia that may occur with hypoglycemic episodes resulting from insulin therapy.

Organic neuritis causes a pain of different magnitude. Symptoms arise either in the peripheral nerves (more commonly in the lower extremities) or in the visceral or autonomic nervous system as nonpainful variations, or in both. This neuropathy is seen in cases of long-standing diabetes with or without significant peripheral vascular occlusive disease; it often is associated with chronic poor diabetic control, although this is not mandatory for its onset.

Figure 1 shows the areas of the nervous system which may be involved in diabetic neuropathy. Involvement of the cranial nerves occurs most commonly within the oculomotor group, with the third and sixth nerves involved most frequently and the fourth and second nerves implicated to a lesser extent. These involvements usually are unilateral, well localized and of abrupt onset. In the upper extremity the ulnar nerve is more susceptible than is the radial or median nerve, and, while involvement of this nerve is of a nature similar to that of nerves in the lower extremity, it occurs much less often. In the lower extremity, involvement occurs more frequently in the peroneal nerve than in the tibial nerve; these nerves are more often involved than is the femoral nerve.

The visceral or autonomic nerves are less commonly involved than are the peripheral nerves, but the examiner's inquisitiveness often determines the frequency with which this condition is observed, since it is in essence a nonpainful neuropathy.

Changes in the spinal cord may result in afflictions of the motor nuclei of the brain stem or of the anterior horn cells, producing a type of symptomatology that could be called a chronic poliomyelitis. A second type, with degeneration of the intramedullary portion of the dorsal root fibers, produces the symptom complex imitating tabes; a third form, with lesions of the posterior and lateral columns, imitates the peripheral symptomatology of pernicious anemia.

Characteristics

Table 2 shows the characteristics of peripheral neuropathy. The first and chief symptom is the sensory involvement causing pain (often burning in character), hyperesthesia, and muscle and skin tenderness. The pain usually is bilateral and symmetric, more distal than proximal, and more severe at night. When ischemia is present the pain is commonly worse with dependency and is associated with rubor of the skin. It should not be forgotten that the nerves of the trunk and upper extremities may be involved in the same manner.

The sense of vibration is one of the earliest lost in neuropathy. While this loss occurs with increasing age in all persons, it is more commonly absent or depressed in the diabetic patient of similar chronologic age. Testing always should be carried out with a low-frequency tuning fork, since it has a longer duration of vibration and a greater intensity of resonance than has the high-frequency tuning fork.

Reduced tendon reflexes are of considerable significance, since the Achilles tendon reflex is absent in only about 5 per cent of nondiabetic persons between 55 and 70 years of age and in only 15 per cent of those over 70 years of age. Motor changes and muscular atrophy are much less common in nonischemic diabetic neuropathy than in the ischemic or thiamine-deficient type.

Table 3 lists the changes associated with autonomic neuropathy. The most prevalent

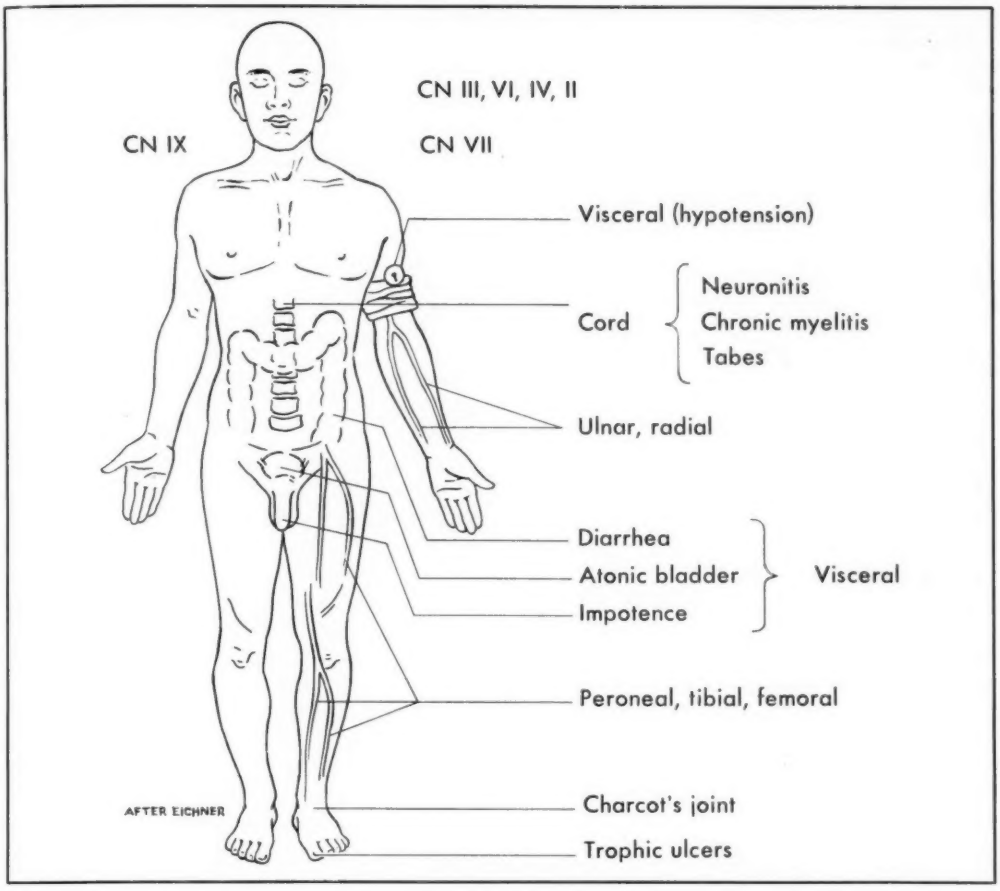

FIGURE 1. Areas of involvement in diabetic neuropathy.

changes are dry, atrophic skin, absence of hair, and loss of sweating. Edema also may be present, and the color of the skin becomes red with dependency but blanches on elevation. This indicates that the corresponding autonomic nerve fibers as well as the sensory peripheral nerve fibers are sufficiently involved to have produced a spontaneous sympathectomy. Recognition of this nonsurgically produced sympathectomy is vital, since surgical sympathectomy will in no way improve vascularity in such an involved area. I believe the most satisfactory test for demonstrating this condition is intra-arterial injection of PRISCOLINE®; this does not cause flushing, cutis anserina or sweating when functional sympathectomy is already present; neither will it produce these symptoms below the level of organic vascular occlusion.

In the cardiovascular system, evidence of spontaneous sympathectomy is common. Orthostatic hypotension and tachycardia occur less frequently and result in complaints of postural dizziness, lightheadedness or weakness. Gastrointestinal symptoms of diarrhea or gastric atonia, with sensations of distention postprandially, anorexia, constipation and achlorhydria, may be found. The urinary system is involved with atonic bladder, and impotence is a frequent complaint in men.

TABLE 2

CHARACTERISTICS OF PERIPHERAL NEUROPATHY

Sensory involvement
Subjective Pain, burning and tenderness, particularly at night
Objective Hyperesthesia, hypesthesia and loss of sense of vibration
Depressed reflexes
Infrequent changes in motor function
Atrophy with ischemia

TABLE 3

CHARACTERISTICS OF AUTONOMIC NEUROPATHY

Skin Dry, atrophic, loss of hair, loss of sweating, edema, red on dependency and white on elevation
Gastrointestinal symptoms Diarrhea, gastric atonia, distention, constipation, achlorhydria
Cardiovascular symptoms Tachycardia, orthostatic hypotension
Genitourinary symptoms Impotence, atonic bladder

Causes

Peripheral nerves are made up of three types of fibers which carry sensations at different rates of speed. The A and B fibers are the largest and most myelinated, and they transmit sensations with the greatest speed. They transmit the sensation of acute pain or the immediate sticking or stabbing phase that we associate with severe pain. The C fibers are thin and unmyelinated and transmit impulses slowly, about one-tenth as rapidly as do the A and B fibers. These impulses result in the second portion of the "double pain" complex, which is experienced as a delayed, diffuse, unpleasant sensation of rather long duration. Demyelination of A and B fibers may occur during poor carbohydrate metabolism or during excessive fat oxidation, which accounts for the loss of the immediate sensation of sharp pain that occurs during uncontrolled diabetes. Lowered levels of phospholipid, cholesterol and cerebroside are found in nerves thus involved in the diabetic patient.

Elevation of the spinal fluid protein may be as high as 500 mg. per cent; however, any elevation suggests the involvement of the nerve root, even when all the symptoms can be ascribed to involvement of the peripheral nerves alone. Any neuropathy extensive enough to involve nerve roots, such as in the Guillain-Barré syndrome, neuronitis or poliomyelitis, produces elevation of the spinal fluid protein; this is true in diabetic neuropathy.

Anatomically, arteriosclerotic changes in the vessels in the nerve area, particularly in the neural nutrient arteries, have been considered a primary cause of diabetic neuropathy, and this is supported by such findings in most neuropathic patients more than 40 years of age. However, it is difficult to accept arteriosclerosis as the sole cause of neuropathy in the presence of rapid recovery from long-standing symptoms or when neuropathy occurs in proximal areas such as the femoral, ulnar and visceral nerves, where arteriosclerotic changes are minor. The fact that neuropathy occurs in about 20 per cent of diabetic patients with peripheral circulatory insufficiency but in less than 10 per cent of non-diabetic persons with similar degrees of peripheral circulatory insufficiency likewise is hard to explain on the basis of arteriosclerosis alone. The most common histologic change is a patchy or nodular degeneration of the myelin sheath; no inflammatory changes are present. If these are the only changes observed, the neuropathy is reversible. While the changes are most noticeable peripherally, they may extend through the lower neurons, including roots and intramedullary prolongations, and cause neuronitis. When loss of the axis cylinder occurs, as it finally does in progressive neuropathy, the condition has reached an irreversible stage.

Vitamin and dietary deficiencies of unknown type also have been implicated in the origin of diabetic neuropathy. Thiamine deficiency is known to interfere with intermediary carbohydrate metabolism and result in elevation of pyruvic and lactic acid blood levels. Thiamine deficiency also can produce hyperglycemia and neuritis in animals, and, while the hyperglycemia may be corrected by

administration of insulin, the animals die of the deficiency state. However, the administration of thiamine does not relieve diabetic neuropathy, and neuropathies due to thiamine deficiency are mostly motor with rather minor sensory involvement. Administration of thiamine to thiamine-deficient animals and human beings results in rapid recovery of lost motor function.

Vitamin B_{12} is implicated by the lowered levels of phospholipids observed in the tissues of animals deficient in this vitamin; the same reduction of phospholipids possibly may occur in the nerves of human beings involved by diabetic neuropathy. The excretion of vitamin B_{12} is greater and its intestinal absorption is less in the diabetic patient with retinopathy than in the diabetic patient who does not have retinopathy. Since neuropathy occurs about three times as frequently in the former type of patient as in the latter, there may well be a significant relationship here. However, even large doses of vitamin B_{12} have been disappointing in treating diabetic neuropathy.

Finally, we must consider the possibility of the occurrence of unknown intermediary metabolites as a cause of diabetic neuropathy. This is suggested by the frequent occurrence of neuropathy in uncontrolled diabetic states, by the quick relief of neuropathy which often follows improvement in the control of the diabetes, by the lack of correlation between the occurrence of neuropathy and the severity of the diabetes, and by the fact that while neuropathy is related to poor diabetic control it is not directly related to the degree of poor control. Hyperglycemia is the only consistent abnormality associated with neuritis which has been reported by all authors, but to date no direct correlation can be made with the degree of hyperglycemia or ketonemia which is present.

Treatment

Treatment of all diabetic neuropathies is aimed primarily toward maintaining blood sugar and electrolytes at as nearly normal levels as possible while keeping the patient on a diet adequate in all elements; however, one will be fortunate to obtain a 50 per cent improvement in organic neuropathy by these means (table 4). In addition to these measures, abstinence from tobacco and the administration of vasodilating agents such as Priscoline and alcohol should be utilized in ischemic neuropathy when it can be demonstrated by intra-arterial injection of Priscoline that this treatment does not impair distal blood flow by excessive dilatation of proximal vascular shunts. Other vasodilators such as ARLIDIN® (nylidrin), papaverine and nicotinic acid are either ineffective or they are uneconomical in comparison.

TABLE 4

TREATMENT OF DIABETIC NEUROPATHY

Treatment of peripheral neuropathy
Control of hyperglycemia
Administration of vasodilators (peripheral-acting and ganglion-blocking agents)
Treatment of visceral neuropathy
Administration of vitamin B_{12}
Nonspecific symptomatic therapy
Administration of anticholinergic agents
Use of parasympathetic stimulators
Use of anti-g suits
General treatment
Care of skin
Relief of pain

Although ganglion-blocking agents are effective in the spastic phase of ischemic neuropathy, they complicate management by inducing orthostatic hypotension when used in therapeutic amounts and are therefore limited to those patients in whom severe hypertension is present. They also cause impotence in men, which may well complete an already poor situation.

With the possible exception of vitamin B_{12}, vitamins have been ineffective in treating neuropathy. In my experience, benefit from vitamin B_{12} has been limited primarily to those patients who have visceral neuropathy. After diarrhea has been stopped by dosages of 4 to 6 mg. weekly, the effectiveness of vitamin B_{12} has been demonstrated by the fact that under conditions of stable diabetic control a weekly injection of 2 mg. will prevent recurrence of diarrhea, while in the same patient an injection of 2 mg. every three or four weeks fails to prevent its recurrence.

Other treatment, such as giving an extract of fetal beef liver or the oral or intravenous administration of salt, is of no value. Diet, antispasmodic and anticholinergic agents, paregoric and bismuth may be necessary to control diarrhea in patients not responsive to vitamin B_{12}. Parasympathetic stimulators may be necessary in atonic states, and parenterally administered vitamin B_{12} and vitamin-B complex may be used, as in deficiency states of the small bowel demonstrated roentgenographically in nondiabetic persons. States of gastric hypochlorhydria are more common in diabetic patients, and they increase the incidence of diarrhea even when neuropathy is not present.

Orthostatic hypotension is managed by various types of anti-g suits, from tight elastic hose to strap-tightened girdles, which are put on before the patient gets out of bed.

Transurethral bladder neck resection may be of benefit to both men and women who have atonic bladder.

The skin breakdown which occurs with neuropathy is treated by maintaining cleanliness, protecting the skin, and use of vasodilators. At times, locally applied steroid ointments are helpful in promoting healing and in relieving pain.

Because of the double vision resulting from cranial nerve palsy, it is necessary for the patient with this disorder, in addition to receiving diabetic therapy, to mask one eye when driving a car or doing other important or dangerous tasks.

Efforts to relieve pain in neuropathy should begin with administration of salicylates and progress to codeine. When codeine is not effective, amputation may be in order; by this time, it will be accepted or even suggested by the patient and made necessary by the condition of the skin or uselessness of the member.

1961

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

Nov. 13-16 Statler Hilton Cleveland, Ohio

Diseases of the Colon in Children

ORVAR SWENSON, M.D.

Professor of Surgery, Northwestern University Medical School, Chicago

In infants and children, abnormalities occur more frequently in the colon than in the small intestine. In the newborn, Hirschsprung's disease is more prevalent than is generally believed and is often misdiagnosed as small bowel obstruction. Imperforate anus and other congenital anomalies of the perineum are quite common. In older children, there are polyps and, most troublesome of all, ulcerative colitis; on rare occasions, regional ileitis is encountered. A résumé of diagnosis and treatment of these conditions will be presented.

Complete program available by writing to Dr. E. S. Hamilton, Program Chairman, Box 1109, Madison 1, Wisconsin.

Campaign for Detecting Cervical Cancer

KURT BOCHNER*

University of Illinois, Chicago

Cancer of the cervix causes more deaths in women than does any other form of cancer. Detecting and eradicating the preinvasive stage of this malignancy is the most potent weapon in combating it.

Cytologic screening of asymptomatic women has led to discovery of 5 to 10 unsuspected malignancies per 1000 patients.

The author reports on an intensive cancer detection campaign conducted at a relatively small air force base.

KURT BOCHNER

CARCINOMA of the cervix represents 11 per cent of the malignancies and is the most common cause of death from cancer in all women. The disease usually begins at the site of the squamocolumnar junction in the cervix, proceeds to break into the underlying stroma, and then invades by direct extension as well as along lymphatic channels and by means of vascular emboli. Cervical carcinoma is internationally classified into four stages, according to the magnitude of invasion that has occurred by the time the patient seeks medical aid. Elaboration of this classification system would be superfluous at this time, since the present discussion will be confined primarily to preinvasive cervical neoplasia.

Three histologically distinct entities have been described in the spectrum between the totally healthy and the truly malignant cervix. The first, squamous metaplasia, is the stage in which the squamocolumnar junction displays replacement and invasion of the columnar epithelium by the squamous cells of the ectocervix. Basal-cell hyperplasia, the second entity, displays a multiplication and heaping up of the basal cells of the cervical epithelium. While there is normally a one or two cell layer of basal cells, in this condition the basal cells multiply rapidly and appear in atypical shapes; however, they maintain a normal nu-

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clear pattern and polarity, and the changes are not evident in the entire epithelial thickness. In the third entity, there are immature, irregularly distributed cells displaying no orderly stratification and manifesting haphazard nuclear polarity. The architecture of the cell layer is completely disrupted; the cells are large and variable in shape, and the nuclei are large, stain deeply, and possess numerous nucleoli. This picture has no semblance of normality, and the only point of differentiation from true malignancy is the absence of a visible invasion of the underlying stroma; hence, this has been labeled preinvasive carcinoma, carcinoma *in situ*, or stage 0 carcinoma of the cervix.

While it is generally believed that squamous metaplasia and basal-cell hyperplasia can and do revert to the normal, it also is almost universally accepted that carcinoma *in situ*, if given time, will progress to invasive carcinoma in the majority of cases. The literature is replete with studies providing evidence for this contention, and the following observations are among the many which support this conclusion.

1. Carcinoma *in situ* has been observed to progress to invasive stages in patients who were not treated at the time of its discovery. Furthermore, retrospective studies of patients who have had invasive malignancies when seen for the first time have disclosed that previous biopsies in these patients had shown the presence of preinvasive carcinoma.

2. Hysterectomy specimens often display invasive carcinoma originating from areas of carcinoma *in situ;* in other cases, the latter lesion also is frequently found at the edges of the invasive lesion.

3. The individual cells of preinvasive and invasive cervical malignancies are identical and indistinguishable.

4. The incidences of the two conditions are parallel at different age levels, the average age of discovery of carcinoma *in situ* being approximately 8 to 10 years earlier than in the case of the lesion which has progressed into the underlying stroma.

5. Groups having a lower incidence of cervical malignancies, e.g., Hebrew women, nuns, etc., also display a similarly low incidence of preinvasive carcinoma.

Thus, we are confronted with a malignancy, carcinoma of the cervix, which takes a huge toll of lives every year. However, removal of the preinvasive stage of this disease offers an almost 100 per cent cure rate, and gynecologists therefore have focused their attention on the detection of carcinoma *in situ* as being the most potent present-day weapon in the struggle to reduce the death toll of cervical malignancies.

While cervical carcinoma can be relegated to the category of preventable diseases, the totally asymptomatic nature of the preinvasive lesion constitutes a major obstacle. Preinvasive and even early invasive cervical malignancies do not cause any bleeding, pain or discomfort, and do not present any visible or palpable lesions. The work of Papanicolaou, however, has enabled us to overcome this barrier. By means of cytologic studies, physicians are able to discover lesions in women who are enjoying excellent health and are free of symptomatology and in whom the cervix appears to be perfectly normal.

Awareness of the lethal potential and absence of symptomatology or visible lesions, or both, of cervical malignancies, combined with the discovery of a means of detecting preinvasive carcinoma, naturally led to advocation of an annual cytologic screening of all women. Cancer detection programs were established at numerous centers, and reports were subsequently published attesting to the value of prophylactic pelvic examinations of asymptomatic women. Physicians were next urged to perform pelvic examinations of and to obtain Papanicolaou smears from all women entering their offices, and to advise them to come back for annual re-examinations. Beecham and Enrich[1] defined the goals of these efforts by stating, "To diagnose cervical cancer early one must assume that all women have a neoplasm and then set out to prove they do not."

In August 1958, a cancer detection campaign was established by the department of obstetrics and gynecology of the 4737 United States Air Force Hospital at Pepperrell Air

Force Base. This department is a relatively small one, rendering gynecologic care to an estimated population of 1500 female dependents of air force personnel and handling an average of 20 deliveries per month. The campaign centered around impressing the population at the base with the value of annual examinations and advertising the fact that the hospital had the facilities to offer this service and was anxious to have all female dependents avail themselves of this opportunity. Notices were published in the *Daily Bulletin* several times each month. Pamphlets obtained from the American Cancer Society were distributed at women's club meetings; spot announcements were made from the base radio station, and the motion-picture film "Time and Two Women" was shown to several groups, at which times the author added a few words and answered questions from the audience.

The response was most gratifying; attendance records at the clinic showed an immediate rise and a persistent large increase over the statistics of the corresponding months during the preceding two year period. The majority of patients were asymptomatic, but others reported irregular bleeding, dysmenorrhea, leukorrhea and other common gynecologic complaints. Patients in the latter group often volunteered the information that they had never thought of coming to see a physician until they became frightened by "all this cancer talk." Every woman was interviewed and was given a pelvic examination, during which two Papanicolaou smears were obtained, one from the vaginal vault and one from the cervical os. In addition, punch biopsies of suspicious cervical lesions were done, and every patient admitted for diagnostic or completion curettage was also subjected to four quadrant cervical punch biopsies.

During the period from September 1958 to August 1959, 618 women were subjected to screening by Papanicolaou smears. Results showed that 590 smears were interpreted as class 1 (no atypical cells present); these patients were advised to return to the clinic after one year or immediately if any abnormal vaginal bleeding occurred during the ensuing year. Twenty-three smears were reported as class 2 (atypical but not malignant); repeat smears obtained from all these women reverted them to class 1. Smears from the remaining five patients were reported as displaying cells suspicious of carcinoma; these were labeled as class 3. Since cytologic screening is not self-diagnostic and merely serves as a tool to indicate the need for tissue examination, four of these five women were admitted to the hospital for cold-knife cervical conization and uterine curettage. Unfortunately, the fifth patient was transferred to another air force base before this could be accomplished, and all efforts to trace this patient's subsequent course have been unsuccessful. Of the four patients subjected to further evaluation, three were discovered to be harboring carcinoma *in situ*, while the fourth was found to have chronic cervicitis.

In summary, 5 of 618 smears were declared to be suspicious of malignancy, giving us an 0.8 per cent rate of discovery of a need for further investigation. Furthermore, even with the elimination of the patient whom we were unable to follow up, the three carcinomas that were detected gave a 0.5 per cent yield of detection of early malignancy as the final result of the campaign. During this same period, one additional carcinoma, which was missed during screening by Papanicolaou smears, was discovered as a result of our policy of obtaining cervical punch biopsies at the time of every dilatation and curettage. The following case reports reveal the asymptomatic and apparently normal status of each of these four patients.

Case Reports

Case 1—A 34 year old Para II came to the gynecology clinic in response to the campaign publicity. The patient's menarche occurred at the age of 10, and she reported 30 day cycles with six days of menstrual bleeding. She denied having any symptoms, including intermenstrual and postcoital bleeding. Pelvic examination failed to disclose any abnormalities; however, the Papanicolaou smear taken from the apparently normal cervix revealed atypical cells suspicious of carcinoma. Cone biopsy of the cervix was performed and car-

cinoma *in situ* was diagnosed. The patient was subjected to total hysterectomy, with wide vaginal cuff excision. No residual malignancy was noted in the latter specimen; hence, this patient was given an excellent prognosis.

Case 2—A 27 year old Para V who sought an annual pelvic examination also denied the presence of any symptoms. Menarche in this patient occurred at age 14; menses recurred every 28 days and lasted four days. Pelvic examination disclosed only moderate cervical erosion, and the Papanicolaou smear was reported as class 3. Cone biopsy of the cervix revealed carcinoma *in situ*, and, since no residual disease was noted in the subsequent hysterectomy specimen, this patient's prognosis is also extremely hopeful.

Case 3—A 31 year old Para V stated that she felt fine and had come to the clinic only because of all the "fuss" being made about annual examinations. Her menarche occurred at the age of 12 and her menses recurred every 28 days, lasting five days. Questioning of the patient disclosed that she had had several episodes of intermenstrual and postcoital bleeding during the preceding 10 months, but she had ignored these symptoms. Pelvic examination was within normal limits except for slight cervical erosion. A class 3 Papanicolaou smear and a cervical punch biopsy report disclosing atypical hyperplasia preceded cold-knife conization of the cervix. The latter led to the discovery of carcinoma *in situ*. Total hysterectomy with wide vaginal cuff resection was performed and no further neoplasia was found at that time.

Case 4—A 34 year old Para III also came to the clinic in response to the campaign publicity. Her menarche occurred at the age of 18, and she had 28 day menstrual cycles with five days of bleeding. The patient stated that she had had progressive dysmenorrhea and menorrhagia since her first delivery. Pelvic examination revealed cervical erosion and a slightly enlarged globular uterus; the Papanicolaou smear was interpreted as being class 1. Because of the progressive menorrhagia combined with anemia, as evidenced by a hemoglobin level of 9.1 gm. per cent and a hematocrit reading of 29 per cent, a dilatation and curettage was done. At this time, four cervical punch biopsies were obtained as part of our routine screening. The pathology report disclosed "midsecretory endometrium and markedly atypical, extensive squamous metaplasia of the cervix." The latter diagnosis warranted further investigation and cold-knife cervical conization was performed. This specimen revealed carcinoma *in situ*, and a total hysterectomy with wide vaginal cuff excision was done. No residual malignancy was noted in the latter specimen. While this case illustrates the fact that Papanicolaou smears are not infallible, it also points to the value of performing cervical punch biopsies at the time that uterine curettage is done. Carcinoma of the cervix may thus be found when not suspected in women undergoing investigation of intrauterine or adnexal disorders as well as in totally asymptomatic women.

Results of Other Surveys

Ullery and Hollenbeck[2] have reviewed the results of a much larger and much more statistically significant survey than the present one. In the former study, 59,712 patients of Columbus County, Ohio, were examined over a two year period, during which annual "well-woman" examinations were widely publicized. The cancer detection rate was found to be 0.34 per cent, with 73 per cent of the afflicted women having revealed no suspicion of malignancy at the time of initial examinations. In another series, Hofmeister, Savage and Wolfe[3] found 52 malignancies during the routine screening of 7,822 patients, thus obtaining a 0.66 per cent detection rate. A review of several other large studies leads one to agree with the conclusion of Andros[4] that ". . . unselected screening of adult women under 50 years of age should result in a detection rate of from 5 to 10 *in situ* lesions per 1000 new patients studied."

Comment

This discussion has been an attempt to illustrate the effectiveness and value of a concerted pelvic cancer detection program among a relatively small female population. Several authors have pointed out that the relatively

small discovery rate of malignancies and the long periods during which no neoplasia is discovered have caused most practitioners to become discouraged with screening studies. Yet, when one realizes that one of every 100 to 200 asymptomatic women examined will be granted a new lease on life, this certainly makes our efforts more than worthwhile.

In closing, the words of Schmitz[5] seem most appropriate: "If the practicing physician will hold all his female patients suspect of harboring a malignancy until he has satisfied himself that no further investigation is necessary, he will be profoundly alarmed and professionally stimulated by the number of unsuspected cervical carcinomas."

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MEETINGS *and Postgraduate Courses*

Columbia University College of Physicians and Surgeons, New York: Symposium on basic problems in neoplastic disease, March 12-14, 1962. For further information, write to: Institute for Cancer Research, Columbia University College of Physicians and Surgeons, 630 West 168th Street, New York 32.

New York Diabetes Association Inc., New York: Ninth annual symposium, on insulin and its use, to be held December 1 at the Hotel Pierre. For further information, write to: Abraham Bluestein, Executive Director, New York Diabetes Association Inc., 104 East 40th Street, New York 16.

New York University Post-Graduate Medical School, New York: Postgraduate courses for practicing physicians and surgeons:

- Diagnosis and therapy of malignant neoplasms of the female genital tract, October 2-6
- Diagnostic cardiac auscultation, October 11-14
- Diagnostic radiology, Wednesdays beginning October 18 (20 sessions in all)
- Electrocardiography, November 6-11
- Symposium on vascular surgery, November 9-11
- Theory and practice of contact lenses, November 9-10
- Surgery of the cornea, November 13-17

For further information, write to: Office of the Associate Dean, New York University Post-Graduate Medical School, 550 First Avenue, New York 16.

State University of Iowa College of Medicine, Iowa City: Postgraduate conferences for 1961 through February 1962:

- Otolaryngology and maxillofacial surgery, November 10, December 13 and January 17
- Cardiac disease, November 17-18
- Respiratory diseases, December 1
- Surgery, December 5-6
- Obstetrics and gynecology, January 9-10
- Refresher course for the general practitioner, February 13-16

For further information, write to: Dr. John Armes Gius, Director, Postgraduate Medical Studies, Office of the Dean, College of Medicine, Iowa City.

Tufts University School of Medicine, Boston: Postgraduate courses for 1961 and 1962:

- Recent advances in internal medicine, October 2-7
- Tutored course in ambulatory medicine, October 20-24 and December 11-16
- Current methods of diagnosis and treatment of cardiac, arterial and venous disorders, January 24-26
- Hematology, March 29-31
- Electrocardiography II, April 23-25
- Neurology, May 3-5

For further information, write to: Dr. Robert P. McCombs, Assistant Dean, Courses for Graduates, Tufts University School of Medicine, 171 Harrison Avenue, Boston 11.

SYMPOSIUM

Effect of Drugs on the Gastrointestinal Tract

ROBERT M. ZOLLINGER,[1] WILLIAM D. DAVIS, JR.[2] AND ANTHONY R. CURRERI[3]

ROBERT M. ZOLLINGER

Topics discussed by the panel include specific indications for use of vitamins, choice of the best sedative and the best antacid for routine use, beneficial effect of anticholinergics, medical versus surgical treatment of hiatus hernia, management of mild cirrhosis, criteria for resumption of activity following hepatitis, treatment of pancreatitis, precautions and technic of needle biopsy of the liver, measures to relieve constipation, preparation of the intestine for surgery, complications of the use of mineral oil, operative management of patients receiving steroids, indications for steroids in gastrointestinal disorders, and drugs to use in the terminal stage of cancer.

DR. ROBERT M. ZOLLINGER (Moderator): It has been said that the gastrointestinal tract is one of the most common sources of distress, and I hope this panel can clarify the use of drugs in such disorders. They are an important item in the cost of medical care.

Vitamins

Dr. Davis, what vitamins, if any, would you prescribe for a patient who tolerates an ordinary diet?

DR. WILLIAM D. DAVIS, JR.: Ordinarily I would not prescribe vitamins for such a patient, unless he insisted on having them, but there are specific indications for the use of vitamins. Hepatic disease, specific vitamin deficiencies, weight-reduction programs and malabsorption syndromes (particularly fat-soluble vitamins in the latter) are good examples.

DR. ZOLLINGER: Do you mean that if I were taking METRECAL® I would also have to take vitamins?

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[2]Associate Professor of Clinical Medicine, Tulane University College of Medicine; Chief of Gastroenterology, Ochsner Clinic and Foundation Hospital, New Orleans, Louisiana.

[3]Professor of Surgery, University of Wisconsin Medical School, Madison, Wisconsin.

Presented before the forty-fifth annual Assembly of the Interstate Postgraduate Medical Association at Pittsburgh.

WILLIAM D. DAVIS, JR.

ANTHONY R. CURRERI

DR. DAVIS: Metrecal has an adequate vitamin content.

DR. ZOLLINGER: What kind of weight-reduction program would this be, polished rice?

DR. DAVIS: An 800 calorie diet.

DR. ZOLLINGER: Do many people get down to 800 calories?

DR. DAVIS: A fair number do; it depends on the motivation.

DR. ZOLLINGER: Dr. Curreri, what type of vitamin therapy do you use for your surgical patients? Every time I walk through the wards I see all those green-colored intravenous bottles. Do people need these vitamins? Do they retain them better intravenously?

DR. ANTHONY R. CURRERI: I feel as Dr. Davis does, that on occasion one is forced to give vitamins or the patient thinks you are not a good doctor. But I am sure that millions of dollars are spent unnecessarily for vitamins which are drained down the sewer.

DR. ZOLLINGER: Do you mean that vitamins go through the body like glucose and salt?

DR. CURRERI: If not needed, they do.

DR. ZOLLINGER: How many physicians in the audience use vitamins every day in their practice? (About two-thirds.) How many do not? (Quite a few.) We have a few strong men left in the profession.

Sedatives

Dr. Davis, what is a good sedative to use for patients who are worried and cannot sleep?

DR. DAVIS: The old stand-by chloral hydrate probably is best for routine use.

DR. ZOLLINGER: Doesn't that agent burn the stomach?

DR. DAVIS: In capsule form it doesn't seem to cause trouble. A capsule contains 0.5 gm. and is smaller than most vitamin capsules.

DR. ZOLLINGER: What do you consider a good dose of chloral hydrate?

DR. DAVIS: From 1 to 1.5 gm., or 2 to 3 capsules, taken at bedtime.

DR. ZOLLINGER: Would you take that rather than SECONAL® or NEMBUTAL®?

DR. DAVIS: Yes, sir.

DR. ZOLLINGER: How long would the effects of chloral hydrate last?

DR. DAVIS: The effects of 1.5 gm. of chloral hydrate last six to eight hours.

DR. ZOLLINGER: Dr. Curreri, what sedative do you use?

DR. CURRERI: Our resident staff usually gives barbiturates, but many of our patients are so used to these drugs that they have to be given chloral hydrate. I would recommend chloral hydrate as the major compound for sleep. A dose of 1.5 gm. will give six to eight hours of good sleep and will not produce hangover as barbiturates do.

DR. ZOLLINGER: I imagine that almost every physician orders the same sedative most of the time. How many physicians in the audience give Seconal? (About one-third.) How many give Nembutal? (Again, about one-third.) How many give chloral hydrate? (About the same number.)

DR. DAVIS: A word of caution should be added: Chloral hydrate should not be mixed with alcohol. This combination is commonly used for Mickey Finns.

DR. ZOLLINGER: In other words, would it be a good sedative to give to an alcoholic patient?

DR. DAVIS: No, sir.

DR. ZOLLINGER: If he had delirium tremens, it would be bad. What would you give?

DR. DAVIS: Paraldehyde.

Antacids

DR. ZOLLINGER: What do you consider to be a good antacid?

DR. DAVIS: It is hard to beat a modification of the old Sippy powder, calcium carbonate and calcium oxide.

DR. ZOLLINGER: Half and half?

DR. DAVIS: Three-fourths and one-fourth.

DR. ZOLLINGER: What about magnesium oxide? That used to be in the night powders.

DR. DAVIS: You are correct. I should have said magnesium oxide instead of calcium oxide. I favor the use of MAALOX®, too, because of its pleasant flavor.

DR. ZOLLINGER: But peppermint empties the stomach, and the medicine has to be taken so frequently. I don't think it is practical.

DR. DAVIS: A 4 oz. bottle is easy to carry in a pocket or purse. It is correct, I think, that peppermint increases the gastric emptying time, but because the medicine is flavorful the patient is more likely to take it regularly.

DR. ZOLLINGER: Would you say, then, that there has been little actual progress in this field since the time of Sippy, and that there is no modern antacid that you prefer to the old Sippy powder?

DR. DAVIS: That is correct, except that we would eliminate the sodium bicarbonate.

DR. ZOLLINGER: Dr. Curreri, do you agree?

DR. CURRERI: I do agree. Despite the fact that we have all these proprietary drugs, we are still doing as many operations for ulcers, if not more, and we are using stricter indications for surgery and therefore I think we have not improved the situation. We live under greater tension, but I do not believe the antacids we have today are any better than those of 15 or 20 years ago.

DR. ZOLLINGER: Could it be that the antacids are better but the patients are defeating their purpose with all the coffee, tea, cola drinks and caffeine-containing drugs?

DR. CURRERI: No. I think the world we live in has been pretty hard on ulcer patients, but, on the other hand—

DR. ZOLLINGER: Fighting Indians was hard, too, and people did not have so many drugs.

DR. CURRERI: But we have other agents we are using with the antacids and still intractable ulcers develop.

DR. DAVIS: I think one other point to emphasize is that we can trust the surgeons a little bit more now. They have become more skillful gastrectomists.

DR. ZOLLINGER: I wish you would put that in writing and send it to all the internists!

I have had the impression, when seeing some ulcer patients who have been referred for operation, that the doctor may have prescribed a good antacid regimen but has not told them to stop drinking coffee and tea, especially on an empty stomach. This results in prolonged overproduction of acid. If a patient drinks coffee, tea, chocolate or cola on an empty stomach, the caffeine content defeats the antacid therapy.

DR. CURRERI: You could add cigarettes and alcohol to that list.

Anticholinergics

DR. ZOLLINGER: What about the anticholinergics? Are they useful?

DR. DAVIS: I think they are extremely useful, both in ulcer disease and ulcerative colitis and, particularly, in functional gastrointestinal difficulty.

DR. ZOLLINGER: What is functional gastrointestinal difficulty? I don't believe such a thing exists.

DR. DAVIS: I am talking about girls who come in with constipation and abdominal pain, diarrhea and abdominal pain, vomiting and abdominal pain, spastic colons, irritable colons —patients with what Bockus calls functional enterocolonopathy.

DR. ZOLLINGER: Oliver Wendell Holmes said the female is a nervous, constipated biped. You are adding some other things to the description.

DR. DAVIS: The two hallmarks are abdominal or intestinal pain and disturbance of bowel regulation.

DR. ZOLLINGER: What do you give such a patient?

DR. DAVIS: We use PAMINE® or Scoline, in a dosage of one 2.5 mg. tablet four times a day. There are a couple of newer anticholinergics that have a longer duration of action; they can be taken only twice a day, and this cuts down the cost. They are DARICON®, which comes in 10 mg. tablets, and AKALON-T®, which comes in 5 mg. and 10 mg. capsules. Disagreeable side effects are dryness of the mouth, mydriasis and, in some elderly men with prostatic trouble, urinary retention.

DR. ZOLLINGER: I thought you said only women have this condition.

DR. DAVIS: Occasionally men do. Some women have to have transurethral resections.

The presence of glaucoma is a contraindication to the use of all these products except BENTYL®, which has no apparent effect on the ocular drainage mechanism. Cardiospasm, I think, is another contraindication. Many of you who are treating ulcer patients with anticholinergics will find that they complain of a burning retrosternal pain. If administration of the anticholinergic is stopped, the pain frequently will disappear; tincture of belladonna can be substituted without causing a recurrence of the symptom.

DR. ZOLLINGER: What causes this pain?

DR. DAVIS: Drug-created spasm of the lower end of the esophagus.

DR. ZOLLINGER: I didn't know that. Any other contraindications?

DR. DAVIS: Pyloric stenosis is a contraindication to the use of anticholinergics.

DR. ZOLLINGER: But you are rather pleased with the anticholinergics and would use them more than you would antacids?

DR. DAVIS: Yes, I would use them more, because we see many more patients with irritable bowel than with ulcer.

Biliary Dyskinesia

DR. ZOLLINGER: Dr. Curreri, is there such a thing as biliary dyskinesia? What about a patient whose cholecystogram is normal but who has pain resembling biliary colic?

DR. CURRERI: I certainly do think there is such a syndrome. Unfortunately the term has received a black eye because it is used whenever there is a question relative to postprandial biliary pain, which may have a host of causes. The incidence of biliary dyskinesia is low. The diagnosis can be made simply by giving the patient a sixth or an eighth of morphine intramuscularly. If the sphincter of Oddi is very sensitive, it will go into spasm, pressure in the common bile duct will rise above 19 cm. of water, and pain will result. If the injection of morphine does not elicit this painful response, the patient does not have biliary dyskinesia.

DR. ZOLLINGER: How long has it been since you saw a case of biliary dyskinesia?

DR. CURRERI: We see probably one every two years.

DR. ZOLLINGER: Dr. Davis, do you believe this hocus-pocus about biliary dyskinesia?

DR. DAVIS: Louisiana must be too hot for these patients. I have never seen a patient who had what I could conscientiously call biliary dyskinesia. Many patients with irritable bowel syndrome have had cholecystectomy in the mistaken hope that it would relieve their pain.

DR. ZOLLINGER: You seem to be a faddist about the subject of the irritable bowel.

DR. DAVIS: I am not a faddist; I just see a lot of it.

DR. CURRERI: The biliary spasm can be overcome by giving amyl nitrite or nitroglycerin. Amyl nitrite will stop the pain precipitously; nitroglycerin will give complete relief within a minute, and relief will last at least one-half to one hour.

DR. ZOLLINGER: So if you have a patient whose biliary tract is free of calculi but who is still having gallbladderlike attacks, you would use nitroglycerin or amyl nitrite to relieve it. If you wanted to investigate further, you would give a hypodermic of morphine, a sixth intramuscularly, and that should induce an attack. Is that right?

DR. CURRERI: That is correct.

DR. ZOLLINGER: How many physicians here have patients at home who have dyskinesia and are giving them trouble? It seems to be fairly common. Dr. Curreri's remarks probably will be helpful.

Someone has asked, Have electrocardiograms shown ischemic changes in these cases of biliary dyskinesia? Would not the nitroglycerin affect this?

DR. CURRERI: All of our patients have had electrocardiograms, but we have found no changes. I must confess there could be such an association. There is no reason why someone with damage to the heart or cardiac area could not have symptoms referable to the gallbladder area.

Hiatus Hernia

DR. ZOLLINGER: Dr. Curreri, do you recommend surgical treatment for hiatus hernia, or is there a place for medical management?

DR. CURRERI: I feel very strongly that there is a place for medical management of hiatus hernia. The diagnosis often is made when the patient has no symptoms related to the hernia, and certainly then nothing should be done. Or a patient who has symptoms may obtain relief by assuming certain positions, such as sitting up rather than lying down postprandially. If the patient has esophagitis or if he has an ulcer with a trapped hernia, he should be treated like any ulcer patient, with a dietary regimen. This group of patients should be treated medically first. If medical management fails, one should consider surgical treatment. But keep in mind that surgical intervention in this condition is attended by morbidity, one of the worst forms being postneuritic pain, particularly if the thoracic approach is used.

DR. ZOLLINGER: Wouldn't you use the abdominal approach?

DR. CURRERI: It is a little harder to correct hiatus hernia that way. We usually employ the thoracic approach. Of course, the symptoms should justify surgery of that magnitude.

DR. ZOLLINGER: Dr. Davis, what would you recommend for a patient who has symptomatic hiatus hernia but refuses operation?

DR. DAVIS: First I would try to reduce his weight; 99 per cent of these patients are overweight.

DR. ZOLLINGER: What formula do you use to determine whether or not a patient is overweight? The standards we use are 112 lb. for a woman and 120 lb. for a man, with 5 lb. added for every inch in height over 5 ft.

DR. DAVIS: In general we use the life insurance tables; however, these are about 5 to 10 lb. too high.

DR. ZOLLINGER: And you would reduce the weight of a patient with hiatus hernia to the ideal level?

DR. DAVIS: It is difficult to reach that level, but we try to get him started in that direction. Weight reduction is very important. The patient may come to surgery in the future, and I think you will agree that it is easier to operate on a nonobese patient. In addition, I think it is important for these patients to sleep in a head-up position, with 8 to 12 in. blocks under the head of the bed.

DR. ZOLLINGER: Isn't that awkward? How do you keep them from sliding off the foot of the bed?

DR. DAVIS: They become accustomed to the position quickly, and it doesn't bother them.

DR. ZOLLINGER: Do you mean that as a medical man you would have people sleeping upside down rather than having an operation?

DR. DAVIS: I think many people would prefer this. How many people in the audience would prefer to sleep in a head-up position rather than have an operation for hiatus hernia? (Practically the entire audience.)

DR. ZOLLINGER: I've been sabotaged!

DR. CURRERI: As a surgeon, I would say amen to that too.

DR. DAVIS: These patients should eat their largest meal in the middle of the day and a small meal in the evening. Never permit them to lie down after eating. An antacid should be taken after meals and, particularly, at bedtime. This is a place for an antacid with the longest possible duration of action and is one instance where, I think, the product GELUSIL-LAC® is worthwhile; ½ oz. taken in milk works quite well for a period of from six to eight hours.

DR. ZOLLINGER: I have been more impressed with the results of surgical treatment of hiatus hernia and am more enthusiastic about it than you are. I do not consider myself radical in my recommendations, but if I had to sleep with 12 in. blocks under the head of my bed and take medication all day long and get up and walk around after meals—I expect I wouldn't have the operation either; I just talked myself out of it!

Cirrhosis

Dr. Davis, what medication would you give a patient who has just a touch of cirrhosis, with spiders on the hands? Do you believe he should take amino acids?

DR. DAVIS: No, sir.

DR. ZOLLINGER: What would you give?

DR. DAVIS: The best medication, of course, is abstinence from alcohol. In second place is good food, particularly protein-containing food, up to the point of protein intoxication—that is, short of hepatic coma.

DR. ZOLLINGER: Wait a minute. What type of food do you mean?

DR. DAVIS: Meat, cheese and eggs. A high-protein diet is extremely helpful to the liver in repairing itself and in mobilization of fatty infiltration, which usually is the pathologic process present in such a case. Brewer's yeast is a very good source of protein and of choline.

DR. ZOLLINGER: How much protein does one get from brewer's yeast?

DR. DAVIS: A tablespoon of brewer's yeast three times a day would supply 20 gm. A vitamin supplement also is worthwhile in a case such as this.

DR. ZOLLINGER: What about skim milk?

DR. DAVIS: It is excellent, with powdered milk added to it. This is an excellent source of protein.

Hepatitis

DR. ZOLLINGER: Is there any drug one can give to a patient who is recovering from hepatitis to help pep him up?

DR. DAVIS: I think a good diet is all that is necessary.

DR. ZOLLINGER: What about the exhaustion? These patients ask for something to pep them up.

DR. DAVIS: This is something that is very difficult to assess. Certainly a small percentage of these patients do have chronic active hepatitis, and the only way to demonstrate this is to get a microscopic section of the liver.

DR. ZOLLINGER: Needle biopsy?

DR. DAVIS: Right.

DR. ZOLLINGER: What are the criteria for resumption of full activity following acute hepatitis in a young man of college age?

DR. DAVIS: First, he must be feeling well. Second, tests must yield normal or stable findings.

DR. ZOLLINGER: What tests?

DR. DAVIS: Let us say the bilirubin is normal, the transaminase is normal, the thymol turbidity is still elevated slightly, and BROMSULPHALEIN® retention is 10 per cent. If these findings remain stable for several weeks, the process probably has become inactive. I would prefer at this time to obtain a needle biopsy, but if facilities for doing this are unavailable I think a trial of full activity should be made, followed by repetition of the same tests. If there is no evidence of worsening, it is safe to resume full activity. The great majority of patients at this stage will have normal test results and can safely resume activity without difficulty.

Pancreatitis

DR. ZOLLINGER: What drugs are helpful in treatment of pancreatitis?

DR. CURRERI: Here, one must think in terms of total treatment. Various etiologic factors may be involved which must be considered. There should be continuous negative suction of the gastrointestinal tract to minimize distention as well as peritoneal irritation. At the same time, one should replace fluids and colloids, since there is such a great loss in the pancreatic area; fluid, plasma and blood should be given if necessary. Administration of cholinergics should be considered, to reduce the flow of secretions and the activity of the bowel. Antibiotics such as chloramphenicol would be useful. For relief of pain, we strongly favor morphine, even though it may produce spasm of the sphincter of Oddi. One might also consider using nitroglycerin. DEMEROL® has been suggested as a substitute for morphine, because it produces less spasm of the sphincter of Oddi, but I feel that Demerol is not as good an analgesic as morphine.

DR. ZOLLINGER: Dr. Davis, what would you do to treat an attack of pancreatitis?

DR. DAVIS: Based on my experience, morphine and Demerol are equally good. We also employ splanchnic block and are satisfied with it from the standpoint of controlling pain.

DR. ZOLLINGER: What do you inject?

DR. DAVIS: Either procaine, 1 per cent, or XYLOCAINE®.

DR. ZOLLINGER: We haven't used splanchnic block for 10 years or so. We have thought that it may increase the blood supply to the pancreas.

DR. DAVIS: We think it may be a good thing to increase the blood supply, in terms of relieving the ischemic necrosis which is important in the pathogenesis and in the end result of pancreatitis.

DR. ZOLLINGER: There is experimental evidence that tends to indicate that there is more damage to the pancreas after the sympathetics have been cut than after vagotomy. How many physicians in the audience use splanchnic block for pancreatitis? (One.)

What about the use of steroids in acute pancreatitis? Steroids are given as a final gesture to everybody. Dr. Curreri, would you use steroids in acute pancreatitis?

DR. CURRERI: No.

DR. DAVIS: Nor would I.

Needle Biopsy of the Liver

DR. ZOLLINGER: Dr. Davis, what are the dangers of needle biopsy, and what precautions are necessary?

DR. DAVIS: The dangers of needle biopsy of the liver are minimal with proper precautions and technic. There must be no interference with the clotting ability of the blood. The prothrombin time must be reasonably good; we prefer a level of 50 per cent of predicted normal, which is about 14.8 seconds with a control of 12 seconds. There must be, to the best of our knowledge, no abscess, no gallbladder immediately beneath, no collection of bile that we would enter with the needle. We attempt to demonstrate this by exploring the area beforehand by infiltration with a long, thin 22 caliber needle as far as the projected path of the biopsy needle. If we encounter pus, a large collection of bile, or a large subsurface blood vessel, we choose another site. Ordinarily, for an intercostal biopsy, we choose a site 2 cm. below the upper border of maximal hepatic dullness on deep expiration. We use expiration to get the lung up out of the gutter when we go through the pleural space.

DR. ZOLLINGER: Isn't there an easier way, down around the costal margin?

DR. DAVIS: Biopsy of a nonpalpable liver is more often successful if one goes transcostally.

DR. ZOLLINGER: What if there are signs of obstructive jaundice with a high alkaline phosphatase?

DR. DAVIS: Some people feel that this is an absolute contraindication to biopsy, and others, myself included, feel that the risk of biopsy in such a situation, where the diagnosis is a real question, is considerably less than the risk of open exploration. However, we have a very alert team of surgeons who can intervene at the first sign of peritonitis.

DR. ZOLLINGER: That's all we do, save you fellows all day long.

Constipation

Dr. Davis, is there actually such a thing as constipation?

DR. DAVIS: Yes. Ninety-nine per cent of it is bad habit combined with spastic colon.

DR. ZOLLINGER: Have you ever cured a patient of constipation?

DR. DAVIS: Many of them.

DR. ZOLLINGER: For how many weeks?

DR. DAVIS: For many years.

DR. ZOLLINGER: What drugs do you give?

DR. DAVIS: We start with the assumption that we do not want to give drugs. The most important single contribution one can make is to take the patient off cathartics, which are the basis of most of the difficulty.

DR. ZOLLINGER: What do you give during the transition period when they stop taking liver pills and start following a diet?

DR. DAVIS: Usually one of the so-called hydrophilic colloids such as KONSYL®, Hydrocil, HYDROLOSE® or METAMUCIL®. The least expensive product is psyllium seed, which may be purchased in a grocery store. The patient is instructed to mix a couple of teaspoons in warm water and drink it. This will prevent the fecal hardening that is the danger if two or three days elapse before there is a normal urge to move the bowels. Sugar and cream can be added to the mixture, if desired.

There are three additional points I should make. (1) It is extremely important to impress on the patient the need to heed the usual postprandial disposition. He should go to the toilet after breakfast, relax, and give himself a chance. (2) If at any time during the day he has an urge to move the bowels, he should pay attention to it rather than suppress it, until he gets the bowel trained again. (3) Finally, this is another area where the anticholinergics are of considerable benefit.

DR. ZOLLINGER: You give an anticholinergic along with the bulk products?

DR. DAVIS: That is right.

DR. ZOLLINGER: What about total water intake?

DR. DAVIS: Adequate fluid is important. We suggest that the patient drink 2 or 3 qt. of liquid in 24 hours.

DR. ZOLLINGER: Can you get a woman to drink that much water?

DR. DAVIS: Most of them will.

DR. ZOLLINGER: Dr. Curreri, do you have anything to add?

DR. CURRERI: No. I go along with Dr. Davis. I use the same agents he does.

Preparation of the Intestine for Surgery

DR. ZOLLINGER: What drugs would you give a patient who is going to have an operation for cancer of the colon? What is the best drug to use to prepare the bowel?

DR. CURRERI: I wouldn't call any drug the "best" drug, but we believe we should cleanse and sterilize the bowel. We do this by giving the patient a liquid diet for three days preoperatively, along with SULFASUXIDINE®, 1 gm. five times a day. Twenty-four hours prior to operation we give neomycin, a total of about 4 gm. in the course of a day.

DR. ZOLLINGER: Is this combination of Sulfasuxidine and neomycin really necessary?

DR. CURRERI: No. Any surgeon who practiced more than 15 years ago will recall that many, many intestinal operations were performed in which there were no infections or abscesses. Nature will control any spillage of bacterial products in the peritoneal cavity at the time of operation, providing it is not continuous. If there is a leak, there will be trouble, and this is where the antibiotics are helpful. If good technic is followed, one need not worry about peritonitis.

DR. ZOLLINGER: So it is the mechanical emptying of the bowel, accomplished by limiting the total intake and by giving Sulfasuxidine (which is really a mild cathartic), rather than a change in bacterial flora that is important. What would happen if we took all of these away from you?

DR. CURRERI: I would rather have cleansing enemas.

DR. ZOLLINGER: Do you have enough nurses in Wisconsin to give enemas?

DR. CURRERI: We still have a few.

Diverticulitis

DR. ZOLLINGER: What drugs do you give to a patient who has diverticulitis? I am talking about the patient who has a little pain in the left lower quadrant from time to time, not about acute diverticulitis with abscess.

DR. DAVIS: The stools should be kept soft, and here again the hydrophilic colloids are useful.

DR. ZOLLINGER: Anticholinergics too?

DR. DAVIS: Sara Jordan thought anticholinergics were important. If there is a little pain or fever, the nonabsorbable sulfonamides are useful.

DR. ZOLLINGER: How long would you give them?

DR. DAVIS: Nine to 10 days.

DR. ZOLLINGER: Would you give them for 10 days, and then withhold them for 10 days?

DR. DAVIS: If repeated courses were necessary I would begin to think about a segmental resection.

DR. ZOLLINGER: He is mellowing! This is one time you would recommend surgery?

DR. DAVIS: Yes.

DR. ZOLLINGER: Have you ever given these patients VASELINE® orally?

DR. DAVIS: No, sir.

DR. ZOLLINGER: How many physicians here have ever seen patients with diverticulitis who have taken Vaseline? (Two.)

DR. CURRERI: What would this do in terms of absorption of vitamins?

DR. ZOLLINGER: I suppose it would raise the devil.

DR. CURRERI: There is pretty good evidence that if mineral oil is taken for long periods the ability to absorb vitamins is reduced.

DR. ZOLLINGER: Which vitamins?

DR. CURRERI: A and K.

DR. DAVIS: A, K and D.

DR. ZOLLINGER: What do you give as replacement?

DR. CURRERI: I don't know. I don't give mineral oil.

DR. DAVIS: Mineral oil is a dangerous prod-

uct. In elderly persons, lipid pneumonia is an extremely dangerous complication of its use that we have seen quite often.

DR. ZOLLINGER: I have been using mineral oil routinely for patients entering the hospital for elective surgical procedures, and now I am told it is almost a poison. How about milk of magnesia? Is it a poison too?

DR. DAVIS: Milk of magnesia is all right on a short-term basis, but it is bad for people with chronic constipation because it increases the irritability of the bowel.

DR. ZOLLINGER: How many physicians in the audience use milk of magnesia? (A majority.) How many tell a patient to take milk of magnesia on a long-term basis? (Very few.) You see, that is different. How many order milk of magnesia once in a while? (Practically all.) How many order mineral oil once in a while? (About a third.)

DR. DAVIS: Mineral oil also predisposes to anal stenosis.

DR. ZOLLINGER: Vitamin deficiency, anal stenosis, pneumonia. Does it cause cancer too?

DR. DAVIS: Not to my knowledge.

DR. CURRERI: It is a carcinogen on the skin; it ought to be the same on the anus.

DR. ZOLLINGER: When I go home I must stop the boys from giving this stuff. I thought it was a mild, innocuous product, and here it is a poison.

Operative Management of Patients Receiving Steroids

Let us say that a patient who has been receiving steroid therapy for ulcerative colitis is being prepared for operation. Do you withdraw the steroid or continue it? There has been a lot of talk about poor wound healing.

DR. CURRERI: Poor adrenal function has been demonstrated in these patients, and therefore they probably will have to continue to take steroid. The operation constitutes an added stress, and therefore at least as much steroid will be needed, if not more.

DR. ZOLLINGER: What do you give?

DR. CURRERI: The usual dosage is 100 units during the operative procedure and then the same amount every eight hours. When the patient's condition stabilizes, dosage is decreased in a steplike manner to a very low level or to total withdrawal.

DR. ZOLLINGER: Do you give supplemental potassium?

DR. CURRERI: If it is needed.

DR. DAVIS: We start with 100 mg. of hydrocortisone intravenously about 8 to 12 hours preoperatively and then give 100 mg. every eight hours through the immediate postoperative period.

DR. ZOLLINGER: One hundred milligrams every eight hours intravenously, starting eight hours before operation and continuing for several days afterward.

DR. DAVIS: Along with potassium, about 40 mEq. per liter, in the intravenous fluid. We check the potassium concentration once a day.

DR. ZOLLINGER: What about the day before operation?

DR. DAVIS: We give potassium triplex, a teaspoon three times a day.

DR. CURRERI: Orange juice contains large amounts of potassium.

DR. DAVIS: Orange juice and meat juice both do, but patients with colitis coming to surgery frequently are not eating well, so we feel a supplement is important.

Regional Ileitis

DR. ZOLLINGER: Dr. Curreri, is there any drug that will help patients who have regional ileitis?

DR. CURRERI: When I see these patients, they have obstruction or abscess and need surgery.

Steroid Therapy in Ulcerative Colitis

DR. ZOLLINGER: Dr. Davis, tell us what conditions of the gastrointestinal tract constitute indications for steroid therapy.

DR. DAVIS: Steroids are extremely helpful in ulcerative colitis, particularly at the time of a severe initial bout.

DR. ZOLLINGER: What dosage would you employ?

DR. DAVIS: In a really severe, fulminating case I would give 15 to 20 units of ACTH daily, administered in an intravenous infusion over a 16 hour period. This is the most potent adrenal steroid stimulation one can get.

DR. ZOLLINGER: Fifteen to 20 units is not a very large dose, is it?

DR. DAVIS: That is exactly the point I wish to make. Administering this small amount of steroid intravenously by drip infusion for 16 to 18 hours provides as potent a stimulation as it is possible to produce. If we did not give the steroid in an intravenous infusion we would give 200 mg. of hydrocortisone initially and then 100 mg. every six to eight hours around the clock.

DR. ZOLLINGER: How can you make the bottle of intravenous fluid last long enough to give 20 units of ACTH over a 16 to 18 hour period?

DR. DAVIS: It is easy. We give the infusion at a rate of 10 to 15 drops a minute.

DR. ZOLLINGER: What do you do on the second day?

DR. DAVIS: We repeat the infusion until the patient begins to go into a remission.

DR. ZOLLINGER: What if he doesn't?

DR. DAVIS: If a patient with acute fulminating colitis does not improve significantly in four days, we think about taking out the colon. In moderately severe colitis we would start with cortisone or hydrocortisone, 100 mg. every four hours, or prednisone by mouth, 10 to 15 mg. four times a day for a total of 40 to 60 mg. a day, plus supplemental potassium, plus AZULFIDINE®, plus anticholinergics, plus vitamins, plus as much food as we can get into the patient.

DR. ZOLLINGER: After the patient is over the acute attack, should he continue to take small doses of steroid?

DR. DAVIS: By and large, we usually come to that. It is necessary to give small doses of prednisone for several months, perhaps 10 mg. a day or 10 mg. twice a day for two to three months.

DR. ZOLLINGER: What else?

DR. DAVIS: Azulfidine, 1.5 gm. four times a day; an anticholinergic (our favorite one is Scoline, 2.5 mg. four times a day); and, ordinarily, Konsyl. We hope the patient's diet will provide 3000 calories a day, and it can contain a little roughage. The diet we use is called a high-caloric, high-protein, medium-residue diet. The patient can have a little lettuce and cooked vegetables if he wants them. We feel that palatability is far more important than any specific limitation.

DR. CURRERI: Since I see the unfavorable effects of this, I would like to ask Dr. Davis about the incidence of perforation from the use of steroids.

DR. DAVIS: Perforation occurred in ulcerative colitis long before steroids were even heard of. I do not believe steroids can be blamed for causing perforation in ulcerative colitis.

DR. CURRERI: I do not agree. I believe the incidence of perforation is much higher now. I am not saying we should not use steroids; they are a great contribution to management of ulcerative colitis, but we should understand and recognize that the incidence of perforation may run higher because of the antiinflammatory reaction.

DR. DAVIS: I am glad he said "may." A number of people disagree with this view.

Drugs to Use in Terminal Cancer

DR. ZOLLINGER: I want to know whether or not cortisone is good for patients who have inoperable carcinoma, if it will make them feel better than morphine does. Is there a place for it here, Dr. Curreri?

DR. CURRERI: Yes, in a terminal state one may use it.

DR. ZOLLINGER: What would you give?

DR. CURRERI: Cortisone, 100 mg. once or twice a day.

DR. ZOLLINGER: Dr. Davis, would you ever do this?

DR. DAVIS: Rarely. I would try THORAZINE® first; I think it will do almost as well.

DR. ZOLLINGER: How much Thorazine would you give?

DR. DAVIS: Fifty milligrams four times a day.

DR. CURRERI: Alcohol will do as well.

DR. ZOLLINGER: Now you are talking! I think we tend to forget the value of alcohol in these situations, don't you agree?

DR. CURRERI: Yes. I think alcohol is something that should be used more often in terminal carcinoma. Cortisone or Thorazine is useful too, and it helps the family if they think you are doing something more than usual.

Use of New Anticancer Drugs

DR. ZOLLINGER: I want to ask Dr. Curreri how he answers the patient who says, "Doctor, I want some of these new drugs." How do you tell him that a certain new drug is good only for mice? This is a serious problem. We are making a lot of progress in the treatment of cancer all the time, and all of us are using these drugs. I think it should be emphasized that there is a place for them but that the indications for their use must be strictly observed and they must be given only under close supervision. Would you agree with this statement?

DR. CURRERI: I agree completely. These compounds are new; they are toxic; they are nearly as toxic to normal cells as they are to cancer cells. Therefore, I think they should always be used in a hospital setting, and probably in a hospital dedicated to this type of investigation.

DR. ZOLLINGER: In other words, you would not give CYTOXAN® or a drug of that type to an ambulant patient?

DR. CURRERI: I would not give Cytoxan to a patient with an intestinal tumor at all, because Cytoxan produces short-term regression, if any. Long-term regressions have been achieved with 5-fluorouracil and 5-FUDR, drugs that are not available to general physicians at present. They may be released for use in the near future, and they should be used with great care and caution.

Selection of Five Drugs

DR. ZOLLINGER: Let us suppose, Dr. Davis, that you were asked to choose only five drugs for all purposes. Which five would you select?

DR. DAVIS: I would select morphine, probably a digitalis preparation, and an antimicrobial drug, perhaps tetracycline. I would want to keep alcohol, too.

DR. ZOLLINGER: What about ether?

DR. DAVIS: I don't do much operating, so I will leave that to Dr. Curreri. The fifth choice would be insulin. I would like to keep an anticholinergic too, if I could.

DR. CURRERI: I would agree with Dr. Davis, but I would replace insulin with ether or some anesthetic that could be used readily in a situation of mass casualties. We have to think about the future, and for this reason I would substitute ether for insulin. But all the others Dr. Davis mentioned would be of tremendous value in practice at any time and at any place in this world.

DR. ZOLLINGER: How many physicians here today would include morphine in such a list of five drugs? (Almost everyone.) How many votes for insulin? (About a third.) How many for digitalis? (Again, almost everyone.) How many for alcohol? (Very few.) How many would vote for a broad-spectrum antibiotic? (The majority.) Alcohol lost out, as you see.

DR. CURRERI: How many would vote for ether? (About two-thirds.)

DR. ZOLLINGER: We were thinking of alcohol in terms of an anesthetic as well.

Chronic Diarrhea

Dr. Davis, how do you treat chronic diarrhea with watery stools?

DR. DAVIS: First one must find the reason for the chronic diarrhea. Treatment depends entirely on the cause. Of all the patients who walk into the office with this complaint, 99 per cent will have an irritable bowel or an antibiotic bowel.

DR. ZOLLINGER: Then you would give an anticholinergic?

DR. DAVIS: I would give an anticholinergic.

DR. ZOLLINGER: On that repetitive note, we will end this discussion. On behalf of the audience, I want to thank Drs. Davis and Curreri for their participation.

Obesity, Drugs and Formula Diets

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ASSIMILATION of foodstuffs is a basic characteristic of animal life. Since the composition of food is inevitably different from body composition, food is never deposited unchanged. In order for absorption to occur, foodstuffs must be reduced to simple components in the intestinal tract. Far-reaching chemical transformations follow absorption of digested food. Part of the transformed food may be oxidized to meet current energy needs; the remainder is stored for short or long periods, depending on the metabolic state of the body. Except for certain essential nutrients, the body is able to synthesize, convert, assimilate, store and mobilize its constituents.

Depot Fat

All three major ingredients of food (carbohydrate, protein and fat) can be stored as depot fat. Certain amounts of each (glucose, amino acids, protein, lipoprotein and chylomicrons) circulate in the blood of the normal individual within a predictable range of concentration. Depot fat may be considered as a reservoir of stored calories in the form of triglycerides, with high caloric density. However, it is becoming increasingly apparent that this reservoir is composed of living cells whose function includes synthesis, storage and mobilization of fat.[1]

The number of calories stored as fat is a function of two variables, energy intake and energy expenditure. Thus, obesity will develop when food intake exceeds energy expended or when energy expenditure falls below energy intake, which is not always obvious. The body of a normal young adult in caloric balance may contain an average of 14 per cent pure fat.[2] A young man weighing 70 kg. may carry approximately 10 kg. of fat, mostly triglycerides. This is approximately two and a half times the weight of his bone minerals.

The relative amount of fat in the body has been shown to increase with age, reaching approximately 25 per cent of body weight in clinically normal men at age 55.[3] In obese individuals, the amount of body fat may be 40 per cent of body weight or even higher. For example, an excessively corpulent, sedentary individual weighing 100 kg. may possess 40

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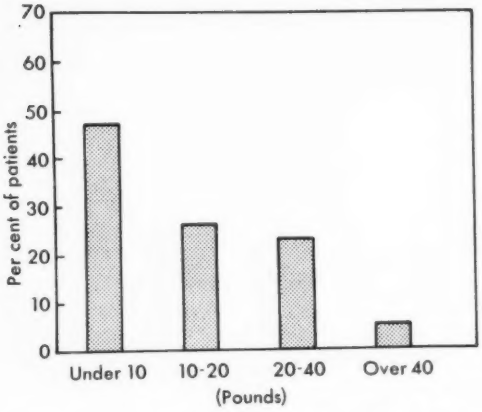

FIGURE 1. Mean weight loss in 1,262 patients treated by various methods.

(Adapted from cumulative tabulations by Stunkard and McLaren-Hume.[4])

kg. of fat, equivalent to 360,000 calories. Theoretically, this individual carries in his body a 400 day supply of calories (calculated at 900 calories per day), all in the form of stored fat. It usually takes years to accumulate such a reservoir of calories. The problem of depleting this hoard down to the 10 per cent level is enormous, and success is not often achieved.

Modes of Treatment

In general, attempts at treating obesity, although numerous and varied, have not been very successful. The results appear particularly discouraging when viewed in the perspective of time.

A cumulative tabulation[4] of seven studies pertaining to treatment of 1,262 obese patients, undertaken between the years 1931 and 1958, showed that only 5 per cent of obese patients lost more than 40 lb., while 47 per cent lost less than 10 lb. Types of treatment included (1) individual instruction and self-selected diet in an employee clinic, (2) a 600 calorie diet prescribed by an internist in private practice, (3) a 900 calorie diet and administration of thyroid extract in a nutrition clinic, (4) administration of dextro-amphetamine sulfate in a diabetes clinic, (5) interview or group discussion in a home economics research setting, (6) a 1000 calorie diet associated with a group psychotherapy project, and (7) interview and diet in an experimental nutrition clinic. The results are summarized in figure 1.

Weight reduction can occur only when the person concerned remains in negative caloric balance. However, negative caloric balance is not easily achieved, particularly since the factors that lead to food intake in excess of energy expenditure are complex and varied. It is becoming increasingly apparent that regulation of food intake is first of all a physiologic phenomenon.[5] It is well known that man maintains his weight at a fairly constant level. This fact has stimulated investigations regarding the physiologic aspects of hunger and satiety,[6,7] in an attempt to elucidate the mechanisms responsible for maintaining body weight at a constant level. If regulation of food intake proves to be a physiologic process, our concept of obesity as a physiologic disturbance in the regulation of food intake will lead to more fruitful areas of investigation. Only through systematic research can we hope to deal effectively with such a complex problem.

Drugs—The task confronting the physician in treating obesity would be far simpler if it were possible to dispense a medication analogous to a diuretic in treatment of edema. Despite the relative ineffectiveness of all drugs thus far given a trial, especially in long-term treatment of obesity, enormous quantities of various drugs continue to be dispensed either with or without a physician's supervision.

The erroneous notion that lack of thyroid hormone produces obesity is an old one. Equivocal metabolic rates in obese subjects have contributed to this theory. Patients with myxedema appear overweight but are not necessarily obese. Lack of thyroid hormone does not produce excessive deposition of fat. There is, however, a sustained accumulation of interstitial fluid which contains a relatively high concentration of protein. When the patient with myxedema is treated with thyroid hormone, a distinct diuresis results, in which the fluid lost has a high nitrogen content. If, following adequate treatment with thyroid, the patient with myxedema (who is now euthy-

roid) remains obese, the obesity is a completely independent problem. In the euthyroid obese individual, administration of a high dosage of thyroid hormone is hazardous. Within the physiologic range, the thyroid gland will decrease its activity in proportion to the dosage of thyroid given.

The potent metabolic stimulators dinitrophenol and dinitrocresol and their derivatives are mentioned only to be condemned. They are too toxic for human use. They remain, however, important tools for experimental studies in metabolism.

The amphetamine derivatives at first may cause a profound decrease in appetite. However, tolerance to them soon develops in the patient, and the dosage must be progressively increased. At higher levels, sympathomimetic effects may be uncomfortable and hazardous. Many patients, including children, have become amphetamine addicts because of the promiscuous use of such drugs.

A valuable study by Van Itallie[8] compared the anorexigenic effects of a hydrophilic colloid preparation with those of a preparation containing amphetamine in 60 obese patients over a 30 week period. Three times daily before meals, alternate patients were given tablets containing 200 mg. of carboxymethylcellulose or tablets, identical in appearance, containing the same amount of carboxymethylcellulose plus 10 mg. of amphetamine. Thirty-five other patients received no medication and served as a control group. All patients were otherwise treated in the same way. The results indicated that the preparation containing the colloid was of no value in weight reduction; in fact, it may have interfered with the patients' reducing regimen. By contrast, the amphetamine seemed to have an anorexigenic effect, particularly during the first six weeks. However, over the entire treatment period of 30 weeks, the amphetamine-treated patients lost only slightly more weight (0.1 lb. per week) than did the control patients, who did not receive any medication. The author concluded that amphetamine is of limited value in treating obesity.

Glucagon is a potent inhibitor of gastric contractions in the rat.[9] The effect is very brief, lasting only a matter of several minutes. Gastric contractions in the rat will return by the time the blood sugar has risen appreciably in response to glucagon. By contrast, a single injection of glucagon in man[10] will induce a more sustained inhibition of gastric contractions (up to 100 minutes). Such an inhibition has been ascribed to increased glucose utilization in response to administration of a single injection of glucagon.

Schulman and associates[11] found in a series of patients in a mental hospital that glucagon, given three times daily, lessened food intake and enhanced weight loss. More recently, Penick and Hinkle[12] reported that a significant depression of food intake in healthy subjects occurred in response to a single injection of glucagon. Such an effect took place two to four hours following glucagon administration, at a time when the arteriovenous glucose differences had returned to postabsorptive levels. The authors observed some clinical clues that gastrointestinal motility was inhibited. If such an inhibition did in fact take place, it would be difficult to reconcile with the more acute inhibition by glucagon of gastric motility, as had been measured directly in man.[10] Moreover, it is most difficult to interpret an acute depression of caloric intake in response to glucagon or any anorexigenic agent when the subject is able to meter the food offered to him because of its familiarity. Penick and Hinkle also reported that two subjects receiving glucagon three times daily lost 1.2 and 0.8 kg., respectively, in six days, which was significant in comparison with control periods.

Glucagon is a potent hormone. Its use in obesity necessitates repeated injections. Such administration of glucagon in man has been shown to produce a diabeteslike syndrome not unlike that seen in response to fasting or carbohydrate privation.[13]

Many drugs have been proposed for treating obesity. Not one stands out as promising; nevertheless, a great many of them are in use. This is not surprising in view of the complexity of factors affecting hunger and satiety. Drugs tend to be attractive to the physician in regard to the ease of dispensing them; however, the physician is not the only one using ineffective drugs. Patients on their own fall

prey to advertising of certain proprietary medications which absolutely guarantee "painless" weight reduction.

Formula diets—A somewhat more "painful" but again "guaranteed" method of weight reduction has been the use of formula diets by our weight-conscious public. The convenience and ease of having a preset amount of food in the form of a formula diet are indeed appealing. The patient's guesswork in assessing caloric intake is eliminated. Perhaps the training and experience of an obese individual in determining caloric density of various foods become unnecessary with formula-type diets. Moreover, the individual can purchase his daily 900 calorie allotment with ease. Efforts to improve the gustatory aspects of such diets to please the discriminating American palate will be continued.

Evolution of formula diets—Formula diets are by no means novel. We are all familiar with the now-established pediatric practice of feeding formula diets as substitutes for mother's milk. In a sense, human milk can be considered a formula-type diet for the infant. Despite the fact that human milk contains approximately half the protein concentration content of cow's milk, it has been assumed that the proteins of human milk are biologically superior. Larger intakes and nitrogen retention for satisfactory infant nutrition are required for cow's milk than for human milk. Breast milk contains slightly more tryptophan and total sulfur amino acids than does casein. However, metabolic studies[14] in man have failed to demonstrate any striking difference in the biologic value of the two proteins. Therefore, with our present knowledge and technics, it is possible to sustain an infant adequately by feeding artificial formula diets of controlled composition. Thus, the human infant was the first beneficiary of the formula diet.

The next major advance in our knowledge of synthetic diets was the discovery of the nutritive value of the amino acids. In 1935, Rose[15] discovered the last essential amino acid threonine. This made it possible to sustain growth and reproduction of rats placed on a nonprotein diet in which the dietary nitrogen was provided from pure amino acids.

In 1940, Mueller et al.[16] achieved an enzymatic digest of casein which would support the growth of experimental animals. Infants and adults were kept in positive nitrogen balance by orally and parenterally administered amino acid mixtures.[17,18] The long-term adequacy of such diets has remained in question. The work of Greenstein and associates[19] has been a remarkable attempt in this direction. These workers have introduced numerous combinations of mixtures of essential and nonessential amino acids that will maintain experimental animals in nitrogen equilibrium over relatively long periods. One such diet has been proposed. Work continues in improving the nutritional significance of these water-soluble, chemically defined diets.

In 1944, Olmsted, Harford and Hampton[20] attempted to construct a formula diet for human use which was free of natural foods and composed of nutritional factors in chemically pure form. A master diet was prepared containing 70 gm. of amino acids derived from a digest of casein, 250 gm. of dextrose, and 140 gm. of fat in the form of a vegetable oil. The elements were added in the form of a salt mixture and included calcium, phosphorus, potassium, sodium, chlorine, magnesium, iron, iodine, manganese, copper and zinc. A polyvitamin preparation also was given as a daily supplement. The purpose for which the formula diet was intended was an elegant one, namely, to treat patients with allergy and to provide low-residue food for patients with certain intestinal disorders. Conceivably, a patient who is sensitive to some natural foods may be temporarily sustained on a formula diet of this type while natural foods are gradually introduced in an attempt to diagnose the sensitizing foods. This is also a well-known pediatric practice.

The danger of missing an important nutrient in the long-term maintenance of patients on formula diets was illustrated by the findings of Register and associates.[21] These workers showed, years after its introduction, that the army K ration had insufficient pyridoxine activity to support normal growth of rats. It is true that virtually all of the important nutrients have now been discovered. It is also true

that the relative amounts of such nutrients in the human diet are subject to continued evaluation and research.

Formula diets as research tool—In 1954, Ahrens, Dole and Blankenhorn[22] introduced the concept that formula diets may be of value in controlled metabolic-nutritional studies in man. This type of diet was invaluable in assessing the influence of various dietary fats on serum lipids.[23-26] During successive feeding periods in man, fat A is isocalorically substituted for fat B. Enough time is allowed to elapse during each period in order to compare the effects on serum lipids of fats A and B. It is evident that during such experimental periods, the protein, carbohydrate, mineral and vitamin contents of the formula have remained constant. In studies of this type, the composition of the formula diets can be manipulated in order to approach, in a gross manner, the composition of the American diet.

The average American diet, according to a summary of the 1955 household consumption survey by the United States Department of Agriculture,[27] derives 44 per cent of its caloric content from fat, 13 per cent from protein, and 43 per cent from carbohydrate. The survey made no deductions for food discarded. Thus, a formula diet can be made in these proportions and used as a research tool. An example of such a diet is shown in figure 2. The ingredients are passed through a dairy-type homogenizer. The minerals and vitamins are either incorporated into the homogenate or added as supplements. Such a formula is an excellent tool for assessing accurate intake of food in metabolic studies. It is invaluable, for example, in protein and electrolyte balance studies in man when an accurate record of intake is clearly needed.

Formula diets and obesity—The use of formula diets as a research tool in metabolic-nutritional studies is obviously valuable. Such diets also can conceivably be manipulated in numerous ways to conform to the objectives of a given research project. For example, it is possible to fashion a formula diet as a daily ration which contains 900 or 1000 calories, with 70 or 80 gm. of protein of good biologic

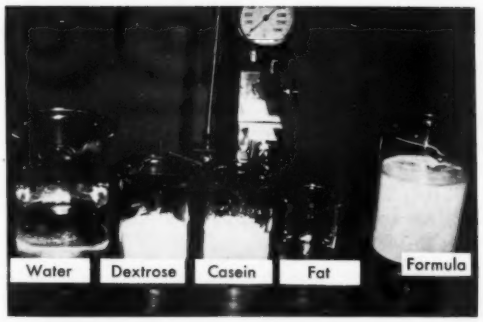

FIGURE 2. Ingredients of homogenized formula diet used in metabolic-nutritional studies in man. Minerals and vitamins can be incorporated into the homogenate or given as supplements.

value, 20 or 30 gm. of fat, and 110 or 120 gm. of carbohydrate. To such basic ingredients, all the known vitamins and minerals can be added. An individual consuming such a diet daily can be expected to lose weight if his caloric expenditure remains in excess of calories consumed. Yet, this latter basic principle applies to any individual consuming subcaloric intake in the form of regular food. This is the position taken in a recent statement by the Council on Foods and Nutrition of the American Medical Association[28] with respect to formula diets and weight control.

It has been argued that it is easier for an obese individual to adhere to a subcaloric formula diet than it is for him to consume regular food in subcaloric amounts. We have witnessed the transfer of formula diets from the research laboratory to the supermarket. The initial acceptance by the public of such diets has been overwhelming. This has been in part due to the fact that subcaloric formula diets have been tailor-made for the obese individual. Such an individual will venture on a diet of any kind for two, three or four weeks, and, let us assume, will lose a significant amount of weight. However, within four weeks of cessation of the formula diet and resumption of regular food, this same individual will find himself reverting to his original obese weight. In a sense, he will have wasted his time and effort. It is the long-term result about which he should be concerned and of which

he remains ignorant. This, in essence, is the tragedy.

Comment

From the preceding discussion, it is evident that a transient reduction in body weight is not the answer to obesity. Regardless of methods of approach, the long-term treatment of obesity has been disappointing. As Mayer[29] pointed out, "To say that obesity is due to overeating, which is true, is also as illuminating as to say that alcoholism is due to overdrinking. . . . But you have not gone one iota further in knowing how to treat the condition."

There is growing evidence that obesity represents a disturbance in the regulation of food intake. Various factors affect food intake. Therefore, the most productive endeavors in the problem of regulating food intake would appear to be those which utilize a variety of disciplines, including nutrition, physiology, biochemistry and psychology. Such a multidisciplinary approach is indeed well justified by the complexity and importance of the problem.

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CLINICOPATHOLOGIC CONFERENCE

Report From Veterans Administration Hospital, Hines, Illinois

Edited by William J. Donnelly, M.D., Chief, Section of Hematology

Osteolytic Lesions and Cardiac Failure

Report of Case

A 67 YEAR old white man was well until the spring of 1959 when weakness and fatigability gradually developed. His physician obtained an excretory urogram and roentgenograms of the gastrointestinal tract and recommended hospitalization for treatment of an "ulcer." The patient preferred to remain at home, despite additional symptoms of weight loss and passage of dark stools.

First hospitalization—On November 28, 1959, the patient entered a private hospital because of a painful swelling in the skin overlying the right scapula. An abstract of the hospital record contains no other information concerning symptoms or physical findings. A roentgenogram of the chest revealed slight enlargement of the heart and minimal pulmonary congestion. Roentgenograms of ribs, dorsal spine, skull and pelvis disclosed diffuse osteoporosis, and multiple osteolytic lesions in the skull. Roentgenologic study of the upper gastrointestinal tract revealed an area of irregularity in the antrum of the stomach which was thought to represent the residuum of the ulcer. Other laboratory data are listed in table 1. The patient was dismissed on December 8 with instructions to continue his bland diet.

Second hospitalization—On February 9, 1960, the patient was admitted to another hospital because of persistent weakness, anorexia, and a weight loss of 40 lb. in the preceding year. He appeared chronically ill. Blood pressure was 120/60 mm. Hg. The pulse rate was 80 per minute. The lungs were normal except for a few crepitant rales in both bases. The heart was normal. The abdomen was normal except for palpation of a firm, nontender edge of the liver three fingerbreadths below the right costal margin and palpation of the tip of the spleen on deep inspiration. Bilateral varicoceles and moderate "benign prostatic hypertrophy" were noted.

Urinary, hematologic and biochemical findings are summarized in table 1. In addition, several urine and blood cultures, febrile agglutination tests and skin tests (histoplasmin, blastomycin, purified protein derivative) gave negative results. A serum cryoglobulin test was negative. Examination of bone marrow revealed slight hypercellularity; the ratio of

TABLE 1

LABORATORY DATA

STUDIES	HOSPITALIZATION						
	First (November 1959)	*Second (February 9-April 5, 1960)*		*Third (April 14-May 20, 1960)*			
		Initial	Subsequent	Initial	May 13	May 18	May 20
Serologic tests for syphilis	Negative	Negative		Negative			
Urinalysis							
Appearance	Yellow			Amber		Amber	
Reaction	Acid			Acid		Acid	
Specific gravity	1.016	1.015		1.004		1.015	
Protein	Trace	2+		4+		4+	
Sugar	0	0		0		0	
Microscopic examination	Negative	Negative		Few white blood cells		Occasional white blood cells	
Bence Jones protein	0	Negative	Negative twice	Negative twice			
Hematologic studies							
Hemoglobin (grams)	10.2	13.4		14.5		16	14
Hematocrit (per cent)	36	42	47-49	45		49	41
Erythrocytes (x 10^6)	4.26					5.3	
Leukocytes (x 10^3)	14.5	9.2	5.1	6.3		6.3	7.2
Polymorphonuclear neutrophils	69	51		69		55	81
Bands	7						4
Metamyelocytes	2						
Lymphocytes	11	16		31		42	12
Monocytes	10	16				2	1
Eosinophils	1	15	5-8			1	2
Eosinophils/mm.^{3}		398					
Platelets (x 10^3)		300		N*			
Erythrocytic sedimentation rate (mm. in one hour)		12		2			
Blood chemistry							
Urea nitrogen (milligrams)	25	12		18.2			
Uric acid (milligrams)			6.1				
Glucose (milligrams)		94		87			
Total protein (grams)	6.8	5.0		6.0			
Albumin	5.3	3.5		3.7			
Globulin	1.5	1.5		2.3			
Calcium (milligrams)	12.2				9.5		
Phosphorus (milligrams)		N			3.5		

normoblasts to leukocytes was approximately 1 to 4, erythropoiesis was normoblastic, granulopoiesis was intact, there was some eosinophilia, and moderate infiltration by cells having characteristics between those of lymphocytes and plasma cells was noted. The hematologist's impression was "atypical lymphoma, multiple myeloma or macroglobulinemia." An immunologic test for Bence Jones proteinuria gave positive results.

On the fourth hospital day there was electrocardiographic evidence of recent anterior myocardial infarction; symptoms of myocardial infarction were absent, but the serum transaminase concentration simultaneously rose to 84 units. The patient was treated in the usual manner, but anticoagulants were not employed because of the laboratory evidence of hepatic disease. Later, congestive failure ensued, but the patient responded well to restriction of sodium, digitalization, chlorothiazide and potassium chloride (3 gm. daily).

TABLE 1 *(Continued)*

LABORATORY DATA

STUDIES	HOSPITALIZATION						
	First (November 1959)	*Second (February 9-April 5, 1960)*		*Third (April 14-May 20, 1960)*			
		Initial	Subsequent	Initial	May 13	May 18	May 20
Alkaline phosphatase (Bodansky units)	7.1	9.3		20.8	13.7	18	
Acid phosphatase (Bodansky units)		N			0.9		
Bilirubin, total (milligrams)		0.76		1.6			
Direct				0.8			
Indirect				0.8			
Cephalin-cholesterol flocculation		0		0			
Thymol turbidity (units)	4	3		1			
Cholesterol (milligrams)					160		
Cholesterol esters (milligrams)					107		
Prothrombin (per cent)	41	36.5		21.7		24.5	
Transaminase (units)		18	84, 72, 64, 42			64	
Sulfobromophthalein (per cent retention)		21.8	18.2			21	
Sodium (milliequivalents per liter)		133	116-136 (130)†				
Potassium (milliequivalents per liter)		5.4	5.2-6.7 (5.6)				
Chloride (milliequivalents per liter)		100	91-110 (100)				
Carbon dioxide (milli-equivalents per liter)		25	25-26				
Quantitative urinary studies							
Calcium per day (milliequivalents)		38.4	18.4, 67				
Potassium per day (milliequivalents)		27.0	39, 54.3				
Sodium per day (milligrams)			65.5				
17-Ketosteroids per day (normal, 5-20 mg.)			3.4				
Porter-Silber chromogens (normal, 3.6-11.6 mg.)			3.5				

*Normal.

†Figures in parentheses represent the mean values of serial determinations.

Because of the equivocal interpretation of the sternal bone marrow, needle biopsy of the liver and biopsy of a lymph node were planned, but these were canceled when the cardiac disease became manifest. Except for a brief episode of cellulitis of the tip of the nose late in March, the remainder of the hospital course was uneventful. The patient was dismissed on April 5, 1960, with instructions to continue taking digitoxin, chlorothiazide and potassium chloride.

Third (Hines) hospitalization—The patient was admitted to Hines Veterans Administration Hospital on April 14, 1960, because of continued weakness and swelling of the feet. The past history included the additional information that he had had gonorrhea many years previously, that he smoked six or seven cigars daily, and that he occasionally drank a "shot" of whiskey or a glass of beer. A brother had died of tuberculosis. Systemic review did not disclose additional symptoms.

Prior to his illness, his average weight was 180 lb. He weighed 142 lb. at the time of admission to the hospital.

Temperature, pulse and respirations were normal. Blood pressure was 116/68 mm. Hg. The eyes, fundi, ears, nose, mouth and throat were normal. About 10 telangiectatic lesions were noted in the mucosa of the inferior aspect of the tongue. The veins in the neck were distended slightly. There was dorsal kyphosis, with an increase in the anteroposterior diameter of the chest. The lungs were hyperresonant to percussion bilaterally, and a few crepitant rales were heard in the right base. The left border of the heart extended to the anterior axillary line. The heart sounds were slightly diminished in loudness. The second aortic and pulmonic sounds were equal, and murmurs were not heard. The firm, nontender, smooth inferior edge of the liver was felt 9 cm. below the right costal margin in the midclavicular line, and the left lobe was felt 7 cm. below the xiphoid. The spleen was not felt. The genitalia and rectum were normal. The stool was yellow-brown and gave a faintly positive reaction to the benzidine test. The extremities were normal except for 3+ pitting edema of the feet and ankles. Neurologic examination did not reveal abnormalities. Peripheral lymphadenopathy was not found.

Results of urinalyses and routine hematologic and biochemical studies are presented in table 1. Examination of the peripheral blood on April 18 revealed moderate anisocytosis, moderate targeting, occasional macrocytosis, and slight poikilocytosis. Platelets and leukocytes appeared normal. Examination of the sternal bone marrow on April 18 revealed moderate hypercellularity; megakaryocytes were normal, the ratio of normoblasts to leukocytes was approximately 2 to 5, erythropoiesis was normoblastic, granulopoiesis was intact, and there was a striking increase in the number of small, lymphocytelike plasma cells, accounting for 40 to 50 per cent of nucleated cells (figure 1). None of the plasma cells were in syncytium. The number of eosinophils was increased slightly. Blood culture on May 20 yielded *Diplococcus pneumoniae*.

An electrocardiogram on April 19 (figure 2) revealed a sinus rhythm (66 per minute), a P-R interval of 0.24 second, and low voltage in all leads. T waves were flat in leads 1, 2, 3, AVR, AVL, AVF, V_1 and V_2, and inverted in V_3, V_4, V_5 and V_6. S-T segments were elevated in V_1 through V_4, the transition zone was shifted to the left, and small Q waves were present in leads 1, 2, AVL, V_5 and V_6. The interpretation was first-degree atrioventricular block, old anterolateral myocardial infarction and diffuse myocardial ischemia. Another electrocardiogram on May 3 revealed similar changes but with prominent notching of P waves in leads 2, 3 and AVF.

Posteroanterior and lateral roentgenograms of the chest on April 19 showed marked cardiac enlargement, probably biventricular, and moderate pulmonary congestion. Roentgenograms of the spine on April 19 showed compression of the bodies of the twelfth dorsal and third lumbar vertebrae as well as diffuse demineralization of the bones. The humeri and femurs were similarly demineralized. Roentgenograms of the skull on April 19 and April 27 showed diffuse mottling due to areas of decreased density throughout the calvaria. On May 18, pathologic fractures of the left anterior fifth and sixth ribs were noted. Roentgenologic study of the lower gastrointestinal tract on May 10 did not reveal abnormalities.

The patient was afebrile throughout his hospitalization. A low-sodium diet (2 gm.), digitoxin (0.1 mg. daily), chlorothiazide (250 mg. twice a day) and potassium chloride (3 gm. daily) were given, and the edema of the ankles and the rales in the base of the right lung disappeared. Slight abdominal distress on April 20 was relieved by an antacid. On several occasions the patient complained of loose stools, and KAOPECTATE® was given. Although ambulatory and free of specific symptoms, he continued to complain of weakness and fatigability. Arrangements were being made to transfer him to a nursing home.

On May 20, at about 4 o'clock in the afternoon, the patient suddenly awoke from a nap with a shaking chill. The rectal temperature was 100.8° F., the pulse was irregular and the rate was 104 per minute, and blood pressure was 110/60 mm. Hg. The lungs were normal,

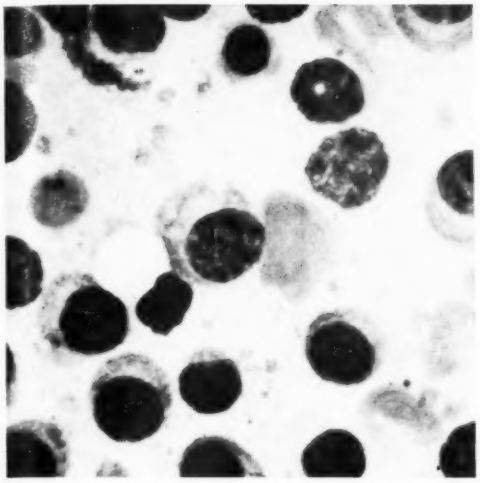

FIGURE 1. Photomicrograph of aspirate of bone marrow showing striking infiltration of marrow by plasma cells and lymphoid plasma cells.

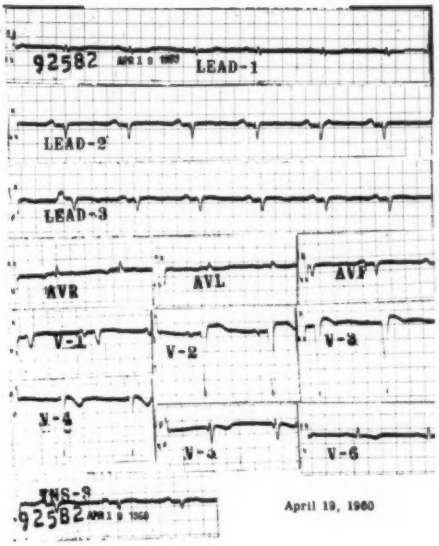

FIGURE 2. Electrocardiogram made on April 19, 1960.

and the heart was unchanged except for an "irregular" rhythm. A sample of blood for culture was taken immediately. Tetracycline, 200 mg., was given intramuscularly. Restlessness increased, and side rails were placed on the bed. A specimen of urine for culture could not be obtained because the patient could not urinate. One 25 mg. intramuscular injection of promazine hydrochloride was given to allay the restlessness. At 6:35 P.M. the patient died.

Discussion

DR. FORD K. HICK (professor of medicine, University of Illinois College of Medicine, Chicago): A 67 year old man became ill in the spring of 1959, with weakness and fatigability. He obviously was studied as an outpatient by someone who performed an intravenous pyelogram and a gastrointestinal series, treated him for an ulcer, and knew of the weight loss and the passage of dark stools. On November 28, 1959, he entered a private hospital because of a painful swelling of the skin overlying the right scapula; this complaint is not mentioned again. Roentgenologic study revealed slight enlargement of the heart and minimal pulmonary congestion, diffuse osteoporosis of the ribs and other bones, and multiple osteolytic lesions in the skull. Here we take the first jump toward a diagnosis; if he didn't have multiple myeloma, he should have had it. An area of irregularity in the antrum of the stomach was thought to represent the residuum of an ulcer. He was dismissed on December 8, with instructions to continue his bland diet.

He entered another hospital on February 9, 1960, because of weakness, anorexia, and a weight loss of 40 lb. He appeared chronically ill and had a normal blood pressure with perhaps a slightly increased pulse pressure, and a few rales in the bases of the lungs. The liver was large. The tip of the spleen apparently was palpable, but later it was not, and so we will pay little attention to this finding. Laboratory studies were very extensive, and I will the hematologist's impression of the bone marrow, which was "atypical lymphoma, multiple skip them for the moment except to mention myeloma or macroglobulinemia." An immunologic test for Bence Jones proteinuria was positive. The other tests for Bence Jones protein reported in the table were of the heat-coagulation and resolution variety. I should like to know whether or not electrophoresis

of the urinary proteins was performed.

On the fourth day an electrocardiogram showed a recent anterior myocardial infarction. Symptoms of infarction were absent, and the diagnosis was supported by elevation of the serum transaminase concentration. There was evidence of hepatic disease. The statement is made that congestive failure ensued. The edema cleared after sodium was restricted and digitalis, chlorothiazide and potassium chloride were given.

At the time of the third hospitalization in April he complained of weakness and swelling of the feet. Apparently he had not lost much weight in recent months; the weight loss of 40 lb. had occurred before his second hospitalization in February. Presumably this means he had an increasing edema, or his weight would have dropped further. Blood pressure was 116/68 mm. Hg. The few telangiectatic lesions in the tongue are difficult to interpret unless similar lesions were seen elsewhere. Dorsal kyphosis is mentioned for the first time, with an increase of the anteroposterior diameter of the chest. Note that he had not complained of pain in the back or chest. A few rales were heard in the base of the right lung, the heart was enlarged to the left, heart sounds were soft, and there were no murmurs. The liver was palpated about 9 cm. below the right costal margin in the midclavicular line and about 7 cm. below the xiphoid. The spleen was not felt. There was 3+ pitting edema of the feet and ankles.

Then the laboratory data are presented, in large batches. Initially the urine contained no albumin or a trace; later the value for albumin was 2+ to 4+. Conventional tests for Bence Jones proteins were repeatedly negative. It is rather remarkable that there was no anemia. Patients with multiple myeloma almost invariably have anemia. How myeloma can be present without anemia I do not know. In November 1959 the hematocrit was 36 per cent, but readings were as high as 49 per cent in April and May 1960. Examination of the bone marrow during this time confirmed the presence of myeloma, with a striking increase in the number of small, lymphocytelike plasma cells, accounting for 40 to 50 per cent of nucleated cells.

The remaining problem is the nature of the involvement of organs other than the bone marrow—the stomach, heart and kidneys—and the mode of death. May we see the roentgenograms?

DR. MIRIAM LIBERSON (physician-in-charge, diagnostic radiology service): A posteroanterior roentgenogram of the chest showed rather marked cardiac enlargement. In the lateral projection, both ventricles appeared to be enlarged. The lung fields were clear. There was moderate kyphosis. Density of all the bones in the chest was decreased. Roentgenograms of the spine showed moderate compression of the bodies of the twelfth dorsal and third lumbar vertebrae. In the upper and lower extremities there was no definitely destructive pathologic process but rather a diffuse decrease in bony density throughout. The skull presented a maximum of pathologic bony involvement; there were so many radiolucent areas that one could hardly see normal bone.

DR. HICK: Do you have films of the stomach available?

DR. LIBERSON: No.

DR. HICK: Osserman[1] recently reviewed the subject of serum protein electrophoresis and emphasized the following points. The usual finding in multiple myeloma is an abnormal peak of proteins either in the beta or in the gamma fraction of the globulin. Usually this peak is sharp, characterized by a height three or four times its width. The abnormal protein, once present, remains until the patient's death. In about 10 per cent of cases of multiple myeloma these peaks fail to develop.

In the present case there was modest elevation of the alpha-2 fraction of the globulin (figure 3). There was no sharp peak of beta-globulin. The gamma-globulin fraction tapered off to a value less than normal. The albumin value was normal.

Uremia did not develop. Total serum proteins remained fairly normal. Total globulin concentration was low and corroborates the electrophoretic data. The value for calcium was a bit high on one occasion but was normal later. Alkaline phosphatase levels rose,

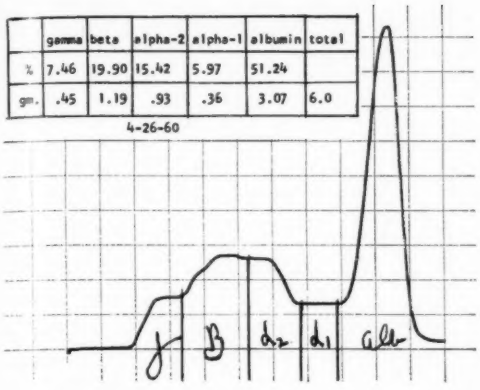

FIGURE 3. Results of paper electrophoresis of serum proteins on April 26, 1960.

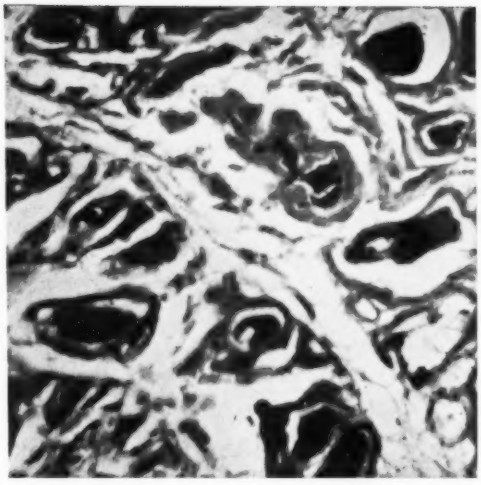

FIGURE 4. Photomicrograph of myocardium showing characteristic interstitial cuffing of atrophic muscle fibers by amyloid (crystal violet stain).

particularly in the later stages of the illness; the concentration of alkaline phosphatase usually is normal in multiple myeloma. Tests of liver function revealed some abnormality, particularly in the prothrombin time. Is the abnormal transaminase value a manifestation of hepatic disease or heart disease? I cannot be sure. The result of the sulfobromophthalein test was distinctly abnormal and is not incompatible with a diagnosis of primary amyloidosis, which I shall discuss in a moment. The serum sodium concentration was quite low; the patient was receiving a low-salt diet part of the time, but a value of 116 mEq. cannot be blamed on a low-salt diet and diuretics unless heart failure was present. The serum potassium value was high, which is rather surprising in view of the good urinary output; note that the patient was receiving potassium during a large portion of this period when the value was elevated. Urinary output of sodium was fairly normal. Urinary output of calcium was excessive but hardly surprising in view of the evidence of bony destruction seen in the roentgenogram.

The usual lesion of the kidneys in multiple myeloma is related in some way to calcium metabolism or to amyloidosis. The amyloidosis of multiple myeloma does not produce a picture of nephrosis as frequently as does the amyloidosis in cases of old tuberculosis or neglected osteomyelitis; however, it can present as nephrosis. This is not classically a case of nephrosis. The serum albumin value was too high, and the concentration of cholesterol was not increased. Yet it presents many of the features of nephrosis. There is no evidence that calcium defects interfered with renal function sufficiently to give rise to this much albuminuria and make it persistent.

The electrocardiograms available to us are dated April 19 and May 3. They are unusual. Although they appear to represent an anterior myocardial infarction because of the QS waves in V_1, V_2 and V_3, there are Q waves in lead 3 and an electric axis greater than -90 degrees. Rarely does one find electrocardiographic axes over -90 degrees in myocardial infarctions; I do not think I have ever seen such a case. Of course the patient may have had more than one infarct. He had at least one affecting the posterior portion of the left ventricle, and another affecting the anterior portion as well. Therefore, he supposedly had two infarcts without pain. I consider this unlikely.

I think this patient had multiple myeloma, manifested primarily by bony lesions and deposits of paramyloid substance in the kidneys and in the heart.

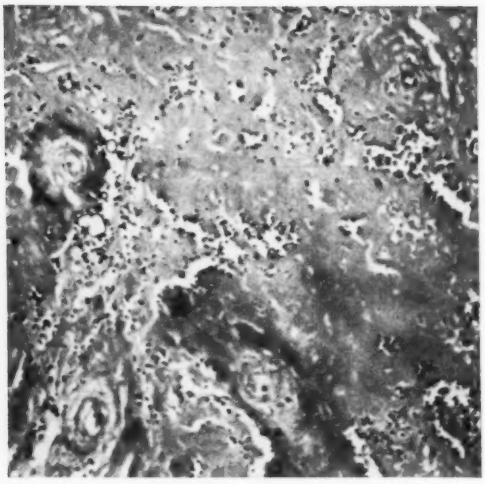

FIGURE 5. Photomicrograph of spleen showing complete obliteration of architecture by amyloid deposition.

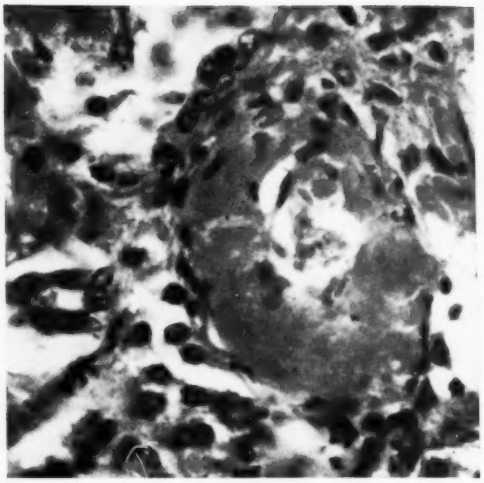

FIGURE 6. Photomicrograph of kidney showing heavy subintimal amyloid deposition.

DR. MYRON E. RUBNITZ (chief, laboratory service): The electrophoretic studies of the serum proteins were made in Dr. Kaplan's laboratory. Dr. Kaplan, would you like to say anything about them?

DR. ERVIN KAPLAN (chief, radioisotope service): We did not consider the electrophoretic pattern of the serum proteins characteristic of multiple myeloma despite the fact that there was slight elevation of the beta and alpha-2 portions.

DR. DEAN DIMICK (assistant section chief, general medical section): The levels of urinary 17-ketosteroids and corticoids, as measured by the Porter-Silber reaction, were somewhat low. These low values could be accounted for by any debilitating disease. However, in this particular patient with myeloma, amyloid infiltration of the adrenal glands is a real possibility. An ACTH test was not done. If the urinary steroid levels failed to increase following the infusion of corticotropin, a diagnosis of relative adrenocortical insufficiency might have been established.

Postmortem Findings

DR. RUBNITZ: The heart was huge, weighing 700 gm. The left ventricular wall was 2.0 cm. thick, and the right ventricular wall was 0.8 cm. thick. The myocardium was abnormally firm, but other abnormalities were not apparent grossly. The cardiac valves were normal. There was minimal coronary arteriosclerosis but certainly not enough to explain the cardiomegaly. Microscopic examination, however, easily explained the enlargement. Throughout most areas the myocardium was heavily infiltrated by an eosinophilic, amorphous material which surrounded the myocardial fibers and had caused severe atrophic changes. The attempts to identify this material disclosed that it stained as amyloid when treated with crystal violet (figure 4). The heart, then, grossly and microscopically appeared like a heart which is involved by primary amyloidosis.

DR. DIMICK: How could this heart have functioned at all?

DR. RUBNITZ: In view of the severe atrophy of the myocardial fibers and the abundance of amyloid, I would have expected more severe myocardial insufficiency clinically.

DR. KAPLAN: Is the amyloid a product of the organ in which it is found or is it transported to the site of involvement?

DR. RUBNITZ: In primary amyloidosis of the heart, without involvement elsewhere in the body, one must assume that the amyloid is

produced in the heart as a result of an unknown type of abnormal protein metabolism. In the more common secondary form of amyloidosis associated with chronic suppurative disease such as tuberculosis or pyelonephritis the amyloid substance must be circulated throughout the body, because of its wide distribution. The distribution of amyloidosis found in cases of multiple myeloma may be that of both primary and secondary types. Amyloid may be either associated intimately with the infiltration of plasma cells or myeloma cells or deposited throughout the body.

Although the gross and microscopic examinations of the heart suggested primary amyloidosis, inspection of other organs and tissues showed widespread changes. The liver was greatly enlarged, weighing 3,040 gm. Its capsule was tense and glistening. The cut surface appeared waxy. Microsections stained with hematoxylin and eosin as well as with crystal violet revealed extensive alteration of the normal architecture by a heavy deposition of a material morphologically similar to that seen in the heart. Scattered throughout many areas were small collections of mononuclear cells, some resembling plasma cells.

The spleen also was involved grossly and microscopically by amyloid. It weighed 510 gm. There was complete effacement of the trabecular and lymphoid pattern by the amorphous amyloid (figure 5). Amyloidosis was also found in the adrenals, kidneys (figure 6), and blood vessels of the pancreas and lungs. Small focal infiltrates of lymphocytes and plasma cells were also found in the kidneys and in the thyroid gland. In the thyroid, the pattern of these cells differed from that seen in instances of subacute or chronic thyroiditis, which usually is accompanied by a granulomatous reaction.

The major involvement by these mononuclear cells occurred in the bony lesions of the ribs and vertebrae that were observed on the roentgenograms. Here the eccentrically placed nuclei of the plasma cells were more apparent. The chromatin clumping of the nuclei and the vacuolation of the cytoplasm of some of the cells provided additional evidence of myeloma. Antemortem aspirates of bone marrow had shown a great increase in plasma cells, some of which had characteristics similar to those found in the bony lesions at necropsy.

Summary of Diagnoses

Clinical diagnoses—Multiple myeloma; coronary arteriosclerotic heart disease, with recent myocardial infarction; amyloidosis of the heart (?).

Dr. Ford K. Hick's diagnoses—Multiple myeloma; amyloidosis of heart and kidneys.

Pathologic diagnoses—Multiple myeloma; amyloidosis of heart, liver, spleen, kidneys, adrenals, and blood vessels of lungs and pancreas.

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CLINICAL STUDY

Guanethidine in the Treatment of Hypertension

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Hahnemann Medical College and Hospital, Philadelphia

Guanethidine is a sympatholytic agent with a hypotensive potency similar to that of the ganglion-blocking compounds. Its effectiveness is further enhanced by the concomitant administration of thiazide derivatives.

The decrease in blood pressure obtained with guanethidine is chiefly a postural response.

A lower incidence of side effects has been observed with guanethidine than with the ganglionoplegic drugs.

Results of a study by the authors have shown that guanethidine is particularly promising for patients with the more severe elevations of diastolic blood pressure.

DURING the past decade, numerous potent antihypertensive drugs have been introduced for treating elevation of diastolic blood pressure. Guanethidine is the most promising recent addition to the growing therapeutic armamentarium. This new drug is a peripheral-acting sympatholytic agent with a hypotensive potency similar to that of the ganglion-blocking compounds but with a lesser incidence of accompanying untoward effects.[1-4] It is the purpose of this report to review the clinical usefulness of guanethidine in the treatment of essential hypertension.

ALBERT N. BREST

Method and Materials

Oral administration—Thirty ambulatory patients with essential hypertension were randomly selected from the hypertension clinic. This group included 14 Negro women, 10 Negro men and six white men. Range in age was from 30 to 68 years. After an initial diagnostic evaluation, the subjects were placed on daily placebo medication for a minimal period of three weeks. During this interval, the patients were seen weekly, at which time blood pressure and physical signs and symptoms were recorded. The control blood pressure was

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greater than 150/100 in each of the 30 subjects studied.

The patients were treated with orally administered guanethidine alone for periods ranging from two to eight months. The initial dosage was 20 to 25 mg. per day. Thereafter, the dosage was increased at weekly or biweekly intervals by 10 to 25 mg. increments until a significant reduction* in orthostatic blood pressure was accomplished. The maximal oral dosage was 150 mg. per day.

Parenteral administration—Guanethidine was administered intravenously to six additional patients, each of whom had blood pressure greater than 150/100. Each patient received 0.125 to 0.25 mg. guanethidine per kilogram of body weight, infused over a 15 minute period. Blood pressure was measured with the patient in both the supine and the erect position every five minutes during the infusion period and every 15 minutes thereafter for at least six hours.

Determination of renal function—In order to assess the effect of guanethidine on renal function, 0.25 mg. guanethidine per kilogram of body weight was administered intravenously to nine hypertensive patients. The glomerular filtration rate, renal blood flow, and water and electrolyte (sodium and potassium) excretion were determined prior to injection, and follow-up studies were performed at 20 minute intervals thereafter for a period of two hours. Inulin was used to measure the glomerular filtration rate, and para-aminohippurate was used to measure renal plasma flow. The excretion rates of sodium and potassium and the concentration of these electrolytes in the plasma were determined concurrently, with a Beckman flame photometer used for analysis.

Results

Oral administration—After receiving orally administered guanethidine, 27 (90 per cent) of the 30 patients achieved a drop in mean arterial blood pressure in the erect position of greater than 20 mm. of mercury; 13 of the 27 became normotensive. In the supine position, 12 patients (40 per cent) achieved a significant reduction in blood pressure; five of the 12 became normotensive (blood pressure of 150/90 or less). Figure 1 shows the mean blood pressure attained. In the 27 patients who responded to guanethidine, the control mean pulse rates before treatment were 80 (supine) and 82 (erect); after treatment, the mean pulse rates were 68 (supine) and 77 (erect). In the three patients who did not respond to this therapy, the control mean pulse rates before treatment were 81 (supine) and 90 (erect); after treatment the mean pulse rates were 66 (supine) and 71 (erect). Statistical data are available which support these findings. The average effective dosage was 70 mg. guanethidine daily. Tolerance to the drug did not develop in any patient.

Dizziness (in nine patients), orthostatic weakness (in eight patients), and diarrhea (in six patients) were the most prominent untoward effects encountered. The diarrhea was manifested as frequency of bowel habit (three to five times daily) rather than loose stools. In addition, failure of ejaculation was noted by 10 of the 16 male subjects; however, impotence did not occur.

Parenteral administration—Five of the six hypertensive patients obtained a significant postural reduction in blood pressure, which began within one to two hours after the intravenous infusion of the drug. The hypotensive response was preceded by an initial elevation of blood pressure in three of the six patients. Thereafter, the blood pressure fell, and the antihypertensive response was frequently prolonged for one or more days. The response which was effected in one patient is shown in figure 2.

Effect on renal hemodynamics—Glomerular filtration rate, renal blood flow, and water and electrolyte (sodium and potassium) excretion were all reduced following intravenous injection of guanethidine (figures 3 and 4). The urine volume and urine sodium excretion were most markedly affected. The reduction in glomerular filtration, renal blood flow, and urine potassium was less pronounced.

*A reduction in mean arterial blood pressure (diastolic pressure plus one-third of the pulse pressure) of at least 20 mm. Hg or the achievement of normotension (150/90) was considered significant.

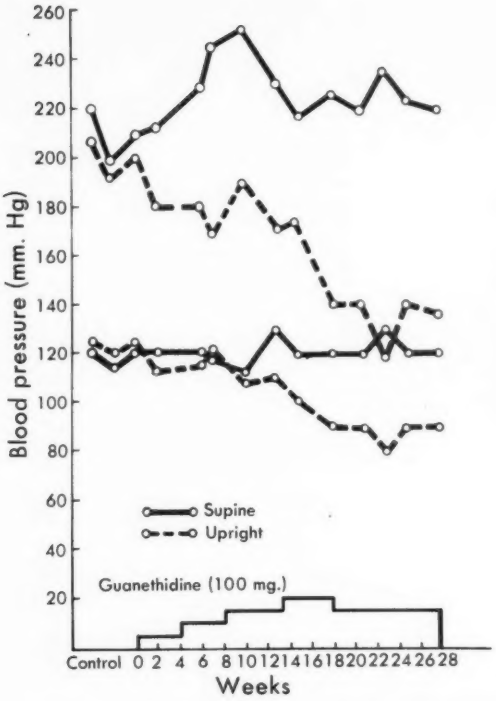

FIGURE 1. Response of blood pressure to orally administered guanethidine. A significant reduction in orthostatic blood pressure was obtained.

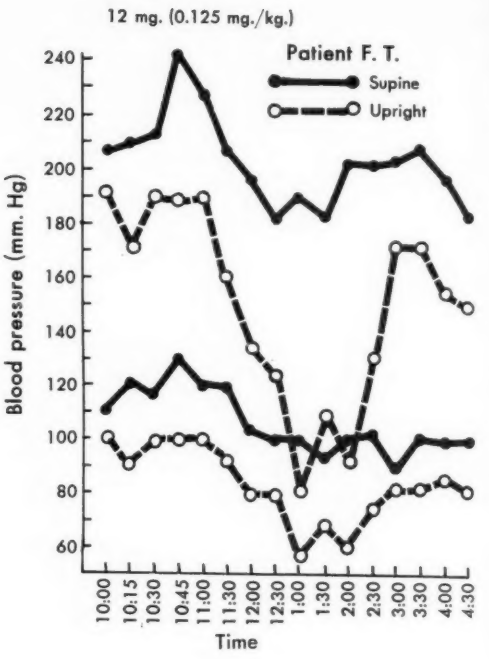

FIGURE 2. Response of blood pressure to intravenously administered guanethidine. Initially, the blood pressure level increased during the infusion of 0.125 mg. guanethidine per kilogram of body weight. This was followed by a marked postural hypotensive response; however, the supine blood pressure was not significantly lowered.[3]

Discussion

The pharmacodynamic studies of Maxwell et al.[5] have demonstrated that guanethidine produces an inhibition of response to electric stimulation of sympathetic nerves. However, there have been no evidences of ganglionic blockade, and the response to injected norepinephrine has not been reduced. It has, therefore, been presumed that this drug prevents the release of norepinephrine from the postganglionic sympathetic nerve endings. This latter mechanism of action is a rather unique one when compared with the pharmacodynamic mechanism of other currently available hypotensive agents.

The present study confirms the potent antihypertensive effectiveness of orally and parenterally administered guanethidine. As with the ganglion-blocking compounds, the hypotensive effect obtained is most marked in the erect position. However, in contrast with the ganglionoplegic drugs, there is a lesser incidence of accompanying side reactions. In addition, parasympatholytic effects are not encountered.

Dizziness, orthostatic weakness and failure of ejaculation are the most prominent untoward effects. The dizziness and orthostatic weakness reflect the therapeutic potency of the drug and probably should not be considered as true side reactions. Both of these effects are most pronounced in the morning, since the patient is usually most relaxed on arising and the level of sympathetic discharge is consequently diminished. Less commonly observed effects are diarrhea and blurring of vision, which reflect relatively unopposed activity of the parasympathetic nervous system.

The antihypertensive effect of guanethidine is usually delayed for 48 to 72 hours follow-

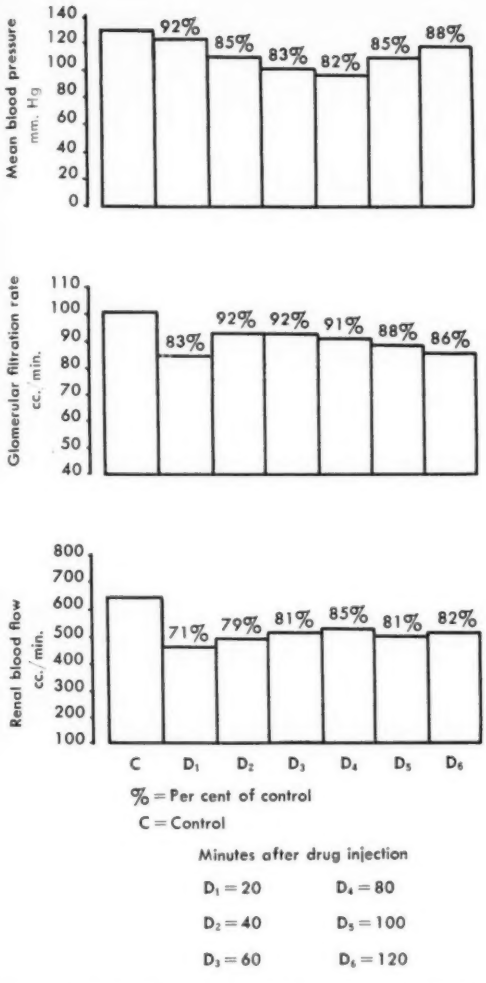

FIGURE 3. Effect of intravenously administered guanethidine on renal hemodynamics. A significant reduction in renal blood flow and glomerular filtration rate accompanied the decrease in mean blood pressure.

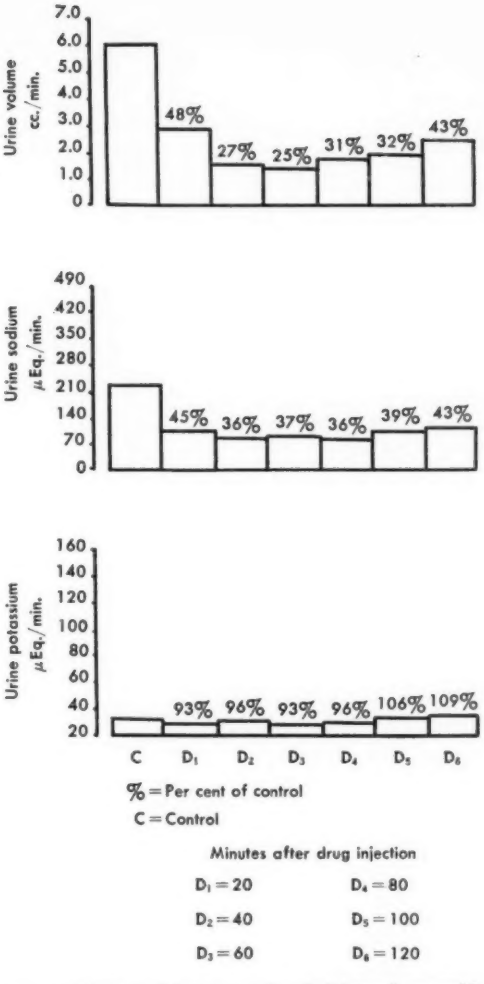

FIGURE 4. Effect of intravenously administered guanethidine on urine volume and electrolyte (sodium and potassium) excretion.

ing oral administration. However, the ensuing reduction of blood pressure is generally prolonged once an effective response has been obtained. Therefore, the drug can be administered in a single daily dose.

In summary, the relatively low incidence of side reactions (particularly, the lack of associated parasympatholytic effects), the prolonged therapeutic response, and the marked hypotensive potency of guanethidine constitute the major therapeutic advantages of this new antihypertensive agent.

The hypotensive potency of guanethidine is markedly potentiated by the therapeutic addition of the thiazide derivatives. In view of the latter effect and since the drug will undoubtedly be used most often in patients who are concurrently receiving thiazide derivatives or *Rauwolfia* or both, it is recommended that orally administered guanethidine be started in an initial dosage of 20 to 25 mg. daily.

Thereafter, the dosage can be increased by 10 mg. increments at weekly intervals until a significant antihypertensive response has been achieved.

Intravenous administration of guanethidine also results in a predominant orthostatic hypotensive effect. Since most patients who require parenterally administered antihypertensive therapy are acutely ill and usually bedfast, the clinical usefulness of this form of guanethidine is therefore limited. The hypotensive response obtained is frequently preceded by an initial elevation of blood pressure, and this effect also detracts from the therapeutic usefulness of intravenous administration. Although the mechanism responsible for the latter effect has not been definitely established, it is most likely caused by an initial release of catecholamines, since the response can be inhibited by pretreatment with phentolamine.

The effect of guanethidine on renal function is qualitatively similar to that observed following the administration of ganglion-blocking agents;[6] i.e., the glomerular filtration, renal blood flow and water and electrolyte excretion are reduced simultaneously although to varying degrees. These findings indicate that the drug must be used with caution in hypertensive patients with accompanying renal impairment.

ACKNOWLEDGMENT

Guanethidine was supplied as ISMELIN® by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

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SCIENTIFIC EXHIBIT

Esophageal Diverticulum

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Introduction

A SERIES of more than 437 cases forms the background but not the basis of our present technic in excising pharyngoesophageal diverticula. Actually, the one stage operation which we will describe has been performed only in the last few years. The developmental period of this surgical procedure was marked by high mortality and morbidity rates, and our patients had most of the complications listed on page 270. Nevertheless, modern methods and precision in technic have evolved to the point that not only are one stage operations feasible and safe but the average period of hospitalization has been reduced to one week.

If the patients with pharyngoesophageal diverticula are not operated on, the symptoms of choking and dysphagia progress until almost nothing can be swallowed, and eventually food material is aspirated, chiefly at night. This results in aspiration pneumonitis, which may have a typical dumbbell formation and often involves the superior segment of the lower lobes of both lungs.

It must be emphasized that since many of these patients are dehydrated, debilitated, and may have pulmonary infection very careful preoperative preparation is essential. Occasionally, preliminary hydration and even tube feeding or gastrostomy may be necessary. Because of the danger of perforation, esophagoscopy is not performed unless an accompanying carcinoma is suspected.

Traction diverticula rarely require operation. These diverticula have wide mouths and empty readily. The declining incidence of tuberculosis may result in still fewer of such cases.

On the other hand, epiphrenal pulsion diverticula often require excision. The difficulties encountered in such cases are illustrated on page 271. Because of frequent association of cardiospasm with the sac and the possibility of pylorospasm, cardiomyotomy and probably pyloroplasty should be done in addition to simple excision.

Adapted from an exhibit at an annual meeting of the American Medical Association, Miami, Florida.

This exhibit received a citation of Honorable Mention in the Scientific Exhibit of the A.M.A. meeting.

Experience

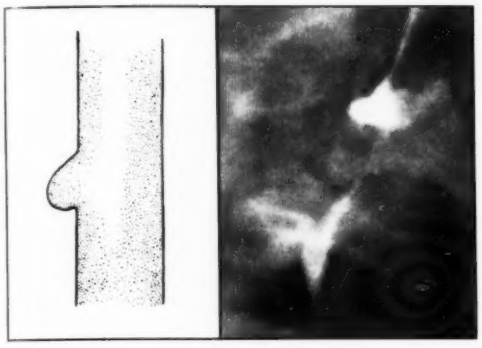
Classification

Epiphrenal
diverticulum.

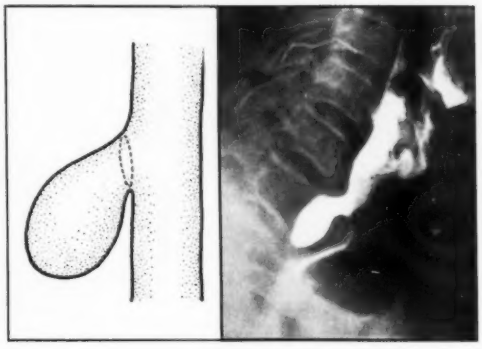
Traction
diverticulum.

Pharyngeal
diverticulum.

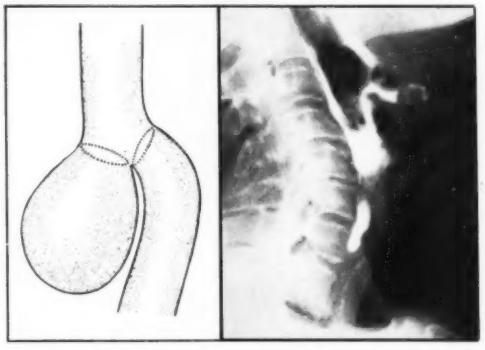
Pathogenesis



Initial stage in development of pulsion pharyngoesophageal diverticulum.



Intermediate stage. Orifice of diverticulum in vertical plane, but sac has become dependent.



Final stage. Note opening into the diverticulum is in transverse plane, while distal opening into esophagus is in vertical plane.

Statistics

Cases of Esophageal Diverticulum	
Pharyngoesophageal	412
Supradiaphragmatic	12
TOTAL	424

Esophageal Diverticulum Recurrence	Cases
Primary operation at Clinic	12
Primary operation elsewhere; recurrence following secondary excision at Clinic	1
TOTAL	13

Technic

General anesthesia is preferred. An incision is made along the anterior border of the left sternocleidomastoid muscle. A collar incision offers little cosmetic advantage. The sternocleidomastoid muscle is retracted laterally, exposing the omohyoid muscle, which is divided, affording entrance into the compartment lateral to the thyroid gland and medial to the carotid artery and internal jugular vein. The inferior thyroid artery and the recurrent laryngeal nerve are dissected out. After the nerve has been carefully identified, the artery is divided.

With the recurrent laryngeal nerve under direct vision, the thyroid gland is rotated medially. The esophagus, which lies on the longus colli muscle, may be identified quickly and surely by the presence of an indwelling Levin tube. At this point, the diverticulum usually will be seen. The bulge representing the sac is picked up with a Babcock-type forceps and elevated into the wound. Generally it can be dissected without difficulty from the surrounding tissue and the esophagus. It is essential that the neck of the pouch be clearly visualized so that it may be precisely demarcated from the esophagus below and the inferior constrictor muscle of the pharynx above.

At this point, again with the recurrent nerve under direct vision, two guide sutures are placed either anteriorly and posteriorly or superiorly and inferiorly to denote the lines of excision. A distal clamp is then placed on the diverticulum and the excision begun. Although it may be argued that an open operation is hazardous, we believe that the added safety of knowing precisely how much of the esophagus is being taken and how much is left outweighs this objection.

If inspection of the interior of the esophagus with special reference to the Levin tube shows clearly that the excision has been begun at exactly the right place, closure with interrupted silk sutures may be started before the sac has been amputated. It is important to leave just a little margin of mucosa beyond the actual esophageal wall to allow for turn-in and to prevent any possibility of stricture. Closure of the mucosal layer is completed in this manner. Placing the knots within the lumen does not seem to have any special advantage. After this first row has been completed, it is comparatively simple to place a reinforcing layer of sutures in the esophageal musculature and in the overhanging inferior constrictor muscle. The use of many sutures of interrupted fine silk effects a secure closure without narrowing the lumen.

The neck may be drained for a day or two to avoid the possible collection of serum in the compartment. This is especially important if the sac is large and has been dissected out of the mediastinum.

Postoperative Care

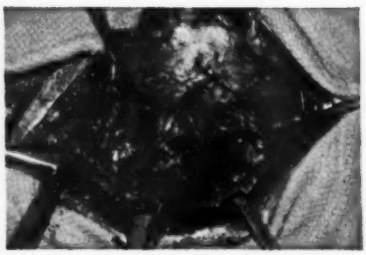
The Levin tube is left in place until it is certain that the patient will not have nausea and vomiting. The newer antiemetic agents have been helpful in this regard. When the stomach has settled down, usually by the following day, the Levin tube is removed and the patient is given sips of water. By the fourth day, a soft diet is tolerated. The patient is cautioned to eat slowly and to chew very thoroughly for a week or two, because the throat is sensitive and some edema may be present.

Antibiotics are not given unless pulmonary infection is associated with the diverticulum. Their use is based on the results of specific bacterial studies of the sputum.

The utilization of this technic has given extremely satisfactory results. None of the complications on page 270 have been encountered in our more recent series of patients.

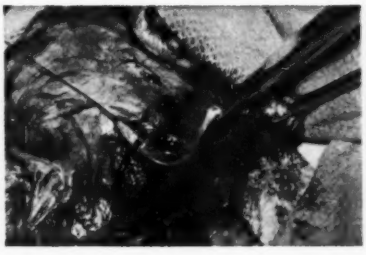
Preliminary exposure. Note omohyoid and prethyroidean muscles.

Omohyoid and prethyroidean muscles divided. Note inferior thyroid artery and common carotid artery.

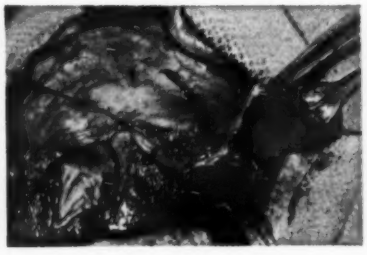


Further dissection of compartment. Note recurrent laryngeal nerve, diverticulum being elevated.

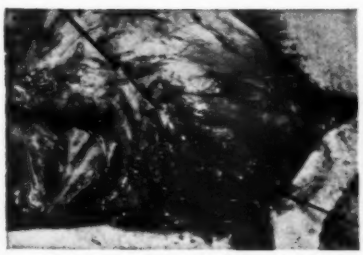
Sac delivered. Separation of sac from inferior constrictor muscle above and esophageal muscle below.



Sac opened. Levin tube within esophagus to guide resection; small cuff left.



First layer of sutures almost completed.



Relationship of operative site to trifurcate recurrent nerve emphasized.

Second layer. Muscles sutured over mucosa, turning it in.

Complete closure.

Results

Complications of Diverticula

Inanition.

"Spillover" pneumonitis.

Carcinoma in a diverticulum.

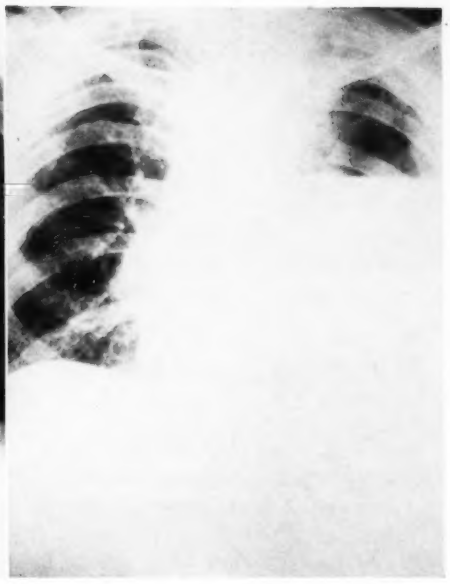
Complications of Surgery

Complications
Mediastinitis
Recurrence
Fistula
Stricture
Recurrent nerve injury

Postoperative Complications	
	Cases
Prolonged fistula	3
Severe stricture	3
Mediastinitis	1
Pneumonitis, lung abscess	1
TOTAL	8

Mortality	
Cases	Deaths
424	2 (0.5 per cent)

Epiphrenal diverticulum
with cardiospasm.



Postoperative rupture of
the suture line.

Epiphrenal diverticulum
with cardiospasm.

Cardia and diverticulum resected;
postoperative pylorospasm.

Self-help Devices:

Homemaking: Opening Containers

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FROZEN foods have reduced considerably, but not eliminated, the need to open jars, cans and bottles, a chore which is often difficult for persons with upper extremity disability. This article focuses on two large groups of disabled persons: those who have only one functioning hand, and those with scattered bilateral upper extremity weakness who must use the combined efforts of both hands.

The major objectives for both of these groups are (1) to provide stabilized openers so that the only functioning hand is free to hold the container, and (2) to find a means of steadying the container so that a second hand is not needed or is free to assist the dominant or working hand.

Without question, electric can openers conserve energy and at first glance would seem to be a ready solution for those with upper extremity involvement. Testing at the Institute of Physical Medicine and Rehabilitation, however, has shown that for some patients the piercing lever requires too much strength; for others the release mechanism is difficult to manage. Some openers have exposed cutting blades and thus are dangerous to use. At this writing, none of the units tested at the Institute have been found sufficiently helpful to the disabled to warrant the higher cost.

For Those Who Must Function Singlehandedly

Many can manage successfully with only one functioning hand by wedging the container either between the knees or in an open drawer (see figure 4).

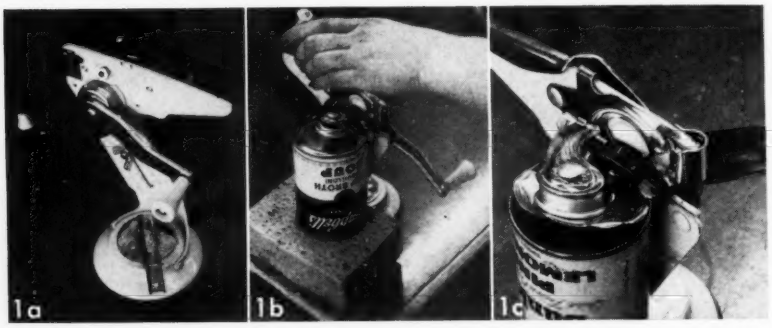

FIGURE 1. The DAZEY® Can Opener has proved particularly satisfactory for those who must function singlehandedly. A lever anchors the unit to a nonporous surface by means of a powerful suction base (a). Sponges can be used as a platform to bring small-sized cans closer to the cutting blade so that there is a minimum of holding (b). A strong magnet holds the cutout lid securely as the homemaker removes the opened can (c).

*Supported at the Institute by the Arthritis and Rheumatism Foundation.

FIGURE 2. The Zim-Twin, which works on a grooved-wedge principle, is effective for removing screw-type jar covers. The jar can be turned with one hand.

FIGURE 3. Bottle caps can be easily removed with one hand by using a wall unit such as the one shown here. The cap falls into a container which is easily removed for emptying.

For Those With Bilateral Hand Weakness or Deformity

Persons with bilateral hand weakness or deformity often have to use both hands to compensate for the loss of strength in the dominant hand. For these persons, large and long handles are helpful in providing greater grasping area for two hands on the handle.

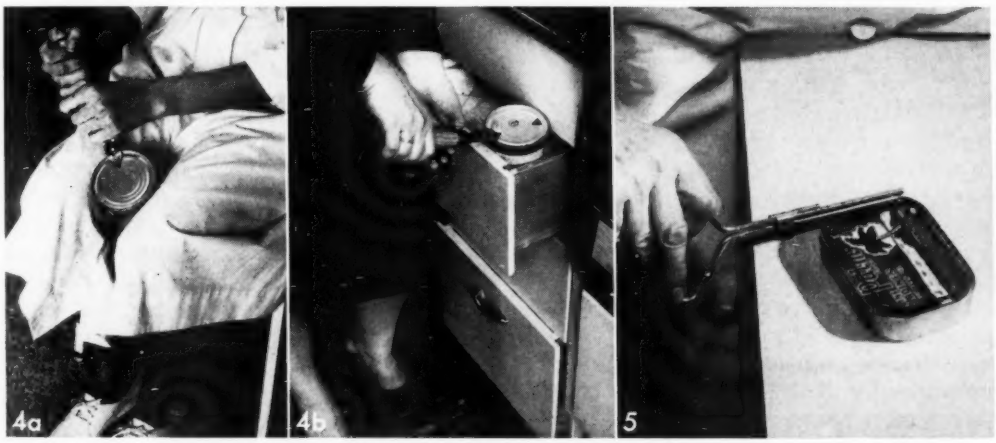

FIGURE 4. Any of the stabilized units described for singlehanded function can be used, or the container can be wedged between the knees (a) or in a drawer (b) so that both hands will be free to exert pressure.

FIGURE 5. Special problems are presented by vacuum-sealed cans in which the key provided is too small for persons with impaired grasp. The oversized Turn-Easy Key offers a larger grasping surface and, therefore, better leverage.

FIGURE 6. Evaporated milk cans are cumbersome for many people to pierce because there is no edge on which to clamp a cutting blade. The Pet Milk Company has a device which fits over the top of the can. A slight blow from a blunt instrument punctures the two holes needed for flow of milk. The cap can then be used as a cover. This device can be obtained by sending 10 cents and a label from a Pet Milk can to the Pet Milk Company, 1418 Arcade Building, St. Louis 1, Missouri.

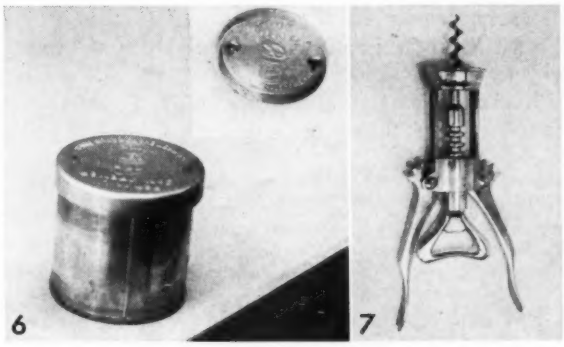

FIGURE 7. For the occasional corked bottle, the Continental Corkscrew works well, but requires the use of two hands.

Medical Color Photography Simplified

BEN R. WILTBERGER*

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BEN R. WILTBERGER

ILLUSTRATIVE art has been recognized since ancient times as an accurate and permanent means of recording medical discoveries. The medical lecturer, too, realizes that his presentation is often more effective when accompanied by illustrations, motion pictures or transparencies. The physician who writes and lectures and who is already familiar with the fundamentals of photography no longer needs to depend on the professional photographer. It is the purpose of this paper to discuss the recent advancements and refinements of the several color films manufactured in the United States which simplify color photography for the physician.

Medical photography requires ground-glass focusing so that the picture is properly framed.

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EDITOR'S NOTE: After this paper was set in type, we were notified that the degree sign is no longer used to express color temperature. The letter K is sufficient.

Although other cameras are satisfactory, the 35 mm. is probably the most practicable. It gives a greater depth of field by virtue of the focal length of the lens. The 20 or 36 exposure film (35 mm.) is economical and is of fine-grain emulsion. It comes in several varieties and insures uniformity of development, a very important factor in experiments. The transparencies are returned mounted and ready for projection. They are lightweight and easy to file. Legends may be written on the wide border. The fine-grain emulsion of the modern 35 mm. color film projects well even in the largest auditoriums. It may be enlarged for publication either as a color engraving or as a black-and-white glossy print.

In color photography, the light source is of primary concern, for light varies in color from the yellow of a candle flame to the light of the clear, blue sky. Lord Kelvin provided a precise method of measuring the color of light by relating it to a black body heated to a given temperature which is expressed in absolute degrees from 0° (0° on the absolute scale is –273° C.). Thus the Kelvin temperature (K) of an object is the temperature in degrees centigrade plus 273°.

Color films available in the United States

FIGURE 1. Tungsten-type view box for roentgenograms or color transparencies.

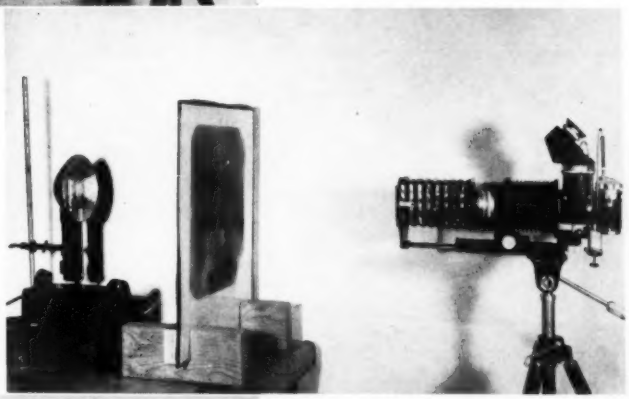

FIGURE 2. Electronic flash with opal glass for copying roentgenograms and color transparencies.

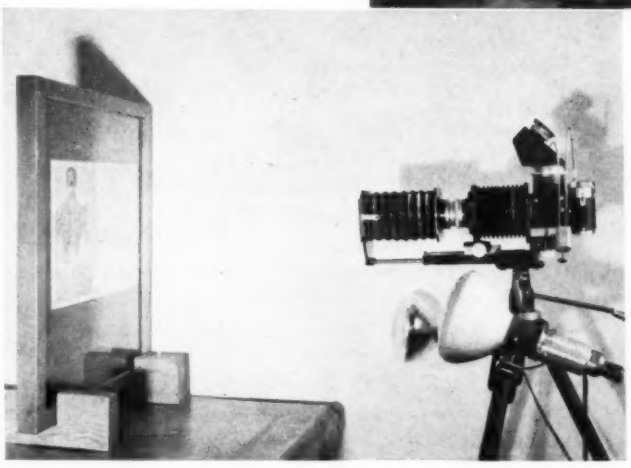

FIGURE 3. Arrangement for copying textbooks or journals.

are balanced to daylight, 6000° K; flash bulbs, 3800° K (type F film); photoflood lamps, 3400° K (professional, type A KODACHROME® film); and studio bulbs, 3200° K (tungsten-type, Super ANSCOCHROME®; tungsten-type, high-speed EKTACHROME® film; and professional-type Anscochrome and Ektachrome films). Although it is often more convenient

TABLE 1

REQUISITES FOR USING KODACHROME FILM IN MEDICAL PHOTOGRAPHY

SUBJECT	TYPE OF FILM		
	Daylight	*Professional, type A*	*Type F*
Patients	Daylight Blue flash bulbs Electronic flash Photoflood lamps, 3400° K, plus 80A filter	Photoflood lamps, 3400° K Daylight plus 85 filter	Clear flash bulbs, 3800° K Photoflood lamps, 3400° K, plus 82A filter Daylight plus 85C filter Studio bulb, 3200° K, plus 82C filter
Gross pathologic specimens	Daylight Blue flash bulbs Electronic flash Photoflood lamps, 3400° K, plus 80A filter	Photoflood lamps, 3400° K Daylight plus 85 filter	Clear flash bulbs, 3800° K Photoflood lamps, 3400° K, plus 82A filter Studio bulb, 3200° K, plus 82C filter Daylight plus 85C filter
Surgical procedures	Blue flash bulbs Electronic flash Photoflood lamps, 3400° K, plus 80A filter	Photoflood lamps or Castle operating room light, 3400° K	Clear flash bulbs, 3800° K Photoflood lamps or Castle operating room lights, 3400° K, plus 82A filter Studio bulb, 3200° K, plus 82C filter
Copying textbooks, color or black and white	Daylight Blue flash bulbs Electronic flash Photoflood lamps, 3400° K, plus 80A filter	Photoflood lamps, 3400° K Daylight plus 85 filter	Clear flash bulbs, 3800° K Photoflood lamps, 3400° K, plus 82A filter Studio bulbs, 3200° K, plus 82C filter Daylight plus 85C filter
Copying color transparencies	Electronic flash plus 81 E F filter	Studio bulbs, 3200° K For flesh tones of patients, 100 W lamp, 2900° K	Photoflood lamps, 3400° K For flesh tones of patients, studio bulbs, 3200° K Project slide on screen and copy (projector lights, 3,190° K)
Copying x-rays	Electronic flash plus 81 E F filter Fluorescent light not recommended	Photoflood lamps, 3400° K, plus CC 10M filter Fluorescent light not recommended	Photoflood lamps, 3400° K Fluorescent light not recommended
Photomicrography	Not recommended	Studio bulb, 3200° K	Photoflood lamps, 3400° K

to use fluorescent lighting in medical photography, it does not always give results consistent with the Kelvin temperature readings.

Of the three color films manufactured in the United States, Kodachrome film has the finest grain and provides the most contrast. However, it has the slowest film speed, and, since it is not developed locally, at least a week must be allowed for processing and mailing. Regular Anscochrome and Ektachrome films have three times the speed of Kodachrome film. They may be developed at home or by a local laboratory in 24 to 48 hours.

Within the last two years, two high-speed color films have been introduced in both daylight and tungsten types. This discussion would be incomplete without a comparison of these films. Super Anscochrome is 10 times as fast as Kodachrome. It has the color fidelity of regular Anscochrome, but has less latitude and a slightly larger grain. The new high-speed Ektachrome, daylight type, is 16 times faster than Kodachrome, and the tungsten type is 12 times faster. They also seem to have more latitude and finer grain than either the Super Anscochrome or the regular Ekta-

TABLE 2

REQUISITES FOR USING EKTACHROME FILM IN MEDICAL PHOTOGRAPHY

SUBJECT	TYPE OF FILM		
	Regular or daylight high-speed film	*Type F*	*High-speed, type B*
Patients	Daylight Blue flash bulbs Electronic flash	Clear flash bulbs, 3800° K Photoflood lamps, 3400° K, plus 82A filter Studio bulb, 3200° K, plus 82C filter	Studio bulb, 3200° K Photoflood lamps, 3400° K, plus 81A filter Daylight plus 85B filter Clear flash bulbs, 3800° K, plus 81C filter Electronic flash plus 85B filter
Gross pathologic specimens	Daylight Blue flash bulbs Electronic flash	Clear flash bulbs, 3800° K Photoflood lamps, 3400° K, plus 82A filter Studio bulb, 3200° K, plus 82C filter	Studio bulb, 3200° K Photoflood lamps, 3400° K, plus 81A filter Daylight plus 85B filter Clear flash bulbs, 3800° K, plus 81C filter Electronic flash plus 85B filter
Surgical procedures	Blue flash bulbs Electronic flash	Clear flash bulbs, 3800° K Photoflood lamps, 3400° K, plus 82A filter Studio bulb, 3200° K, plus 82C filter	Studio bulb, 3200° K Photoflood or Castle operating room lights, 3400° K, plus 81A filter Clear flash bulbs, 3800° K, plus 81C filter Electronic flash plus 85B filter
Copying textbooks, color or black and white	Daylight Blue flash bulbs Electronic flash	Clear flash bulbs, 3800° K Photoflood lamps, 3400° K, plus 82A filter Studio bulbs, 3200° K, plus 82C filter	Studio bulbs, 3200° K Photoflood lamps, 3400° K, plus 81A filter Daylight plus 85B filter Clear flash bulbs, 3800° K, plus 81C filter Electronic flash plus 85B filter
Copying color transparencies	Electronic flash plus 81 E F filter	Photoflood lamps, 3400° K, plus 82A filter Project slide on screen and copy (projector lights, 3,190° K)	Regular 40 W lamp, 2800° K plus 81 E F filter Project slide on screen and copy (projector lights, 3,190° K)
Copying x-rays	Electronic flash Daylight fluorescent lamps (a) plus 81 E F filter for regular type (b) plus CC 10R filter for high-speed type plus CC 10M filter	Photoflood lamp, 3400° K, plus 82A filter Daylight fluorescent lamps plus 85 filter plus 85C filter	Regular 100 W lamp, 2900° K, plus CC 10M filter Fluorescent light not recommended
Photomicrography	Not recommended	Photoflood lamp, 3400° K, plus 82A filter	Regular 100 W lamp, 2900° K

chrome. The color balance of the new high-speed Ektachrome film resembles that of Kodachrome.

For taking color transparencies or movies of patients, pathologic specimens or operative procedures, all three films may be used as directed by the manufacturer for specific lighting conditions. (The Castle operating room light is balanced at 3400° K.) In the copying of x-rays, microscope slides and other color transparencies, these objects act as color filters, and often change the Kelvin temperature of

TABLE 3

REQUISITES FOR USING ANSCOCHROME AND SUPER ANSCOCHROME FILM IN MEDICAL PHOTOGRAPHY

SUBJECT	TYPE OF FILM	
	Anscochrome and Super Anscochrome daylight-type film	*Super Anscochrome tungsten-type film*
Patients	Daylight Blue flash bulbs Electronic flash Photoflood lamps, 3400° K, plus 80A filter	Studio bulbs, 3200° K Photoflood lamps, 3400° K, plus 81A filter Clear flash bulbs, 3800° K, plus 81D filter Daylight plus 85B filter
Gross pathologic specimens	Daylight Blue flash bulbs Electronic flash Photoflood lamps, 3400° K, plus 80A filter	Studio bulbs, 3200° K Photoflood lamps, 3400° K, plus 81A filter Clear flash bulbs, 3800° K, plus 81D filter Daylight plus 85B filter
Surgical procedures	Blue flash bulbs Electronic flash Photoflood lamps or Castle operating room lights, 3400° K, plus 80A filter	Studio bulbs, 3200° K Photoflood lamps or Castle operating room lights, 3400° K, plus 81A filter Clear flash bulbs, 3800° K, plus 81D filter
Copying textbooks, color or black and white	Daylight Blue flash bulbs Electronic flash Photoflood lamps, 3400° K, plus 80A filter	Studio bulbs, 3200° K Photoflood lamps, 3400° K, plus 81A filter Clear flash bulbs, 3800° K, plus 81D filter Daylight plus 85B filter
Copying color transparencies	Electronic flash plus 81 E F filter	Ordinary 100 W house light bulb, 2900° K
Copying x-rays	Electronic flash Daylight fluorescent lamps plus 81 E F filter	Ordinary 40 W house light bulb, 2800° K Daylight fluorescent lamps plus 85 plus 85C filters
Photomicrography	Not recommended	Ordinary 100 W house light bulb, 2900° K

the original light source. Tables 1 through 3 show how each color transparency film manufactured in the United States may be satisfactorily used in medical photography.

Ordinary x-ray view boxes usually have daylight-type fluorescent lamps and may be used with fair results, as suggested in tables 1 through 3; however, the tungsten-type view box (figure 1) gives better results. The light-meter reading is taken from the gray portions of the roentgenograms, excluding from consideration the darkest and lightest areas. An alternative method of copying roentgenograms and color transparencies is shown in figure 2. The electronic flash is placed at a predetermined distance (learned by trial and error) behind the opal glass with the roentgenogram or transparency. For small electronic flash units (50 to 75 watt-seconds), try placing the flash head 6 in. away from the opal glass for Kodachrome film, 8 in. away for Anscochrome and Ektachrome film, 16 in. away for Super Anscochrome film, and 24 in. away for high-speed Ektachrome film.

Figure 3 illustrates the method of copying textbooks or journals. The material to be copied should be in a glass cassette or improvised pressed-glass arrangement to assure uniform focusing. Two light sources with reflectors, to prevent hot spots, should be directed at about a 45 degree angle to the material being copied. A reflected light-meter reading is then taken from several inches away, so it will be out of the shadow of the light meter.

Experimentation with Kodak grain-positive and direct-positive film and with Kodak Micro-File film in the black-and-white copying of x-rays seems to produce copies which are inferior in contrast and detail to those made with the color films previously mentioned.

Summary

1. The new fine-grain color film makes it possible for the physician to do his own medi-

cal macrophotography, photomicrography and microphotography.

2. Ground-glass focusing, which properly frames the picture, is a necessity in medical photography.

3. The 35 mm. camera is the most practicable one for use in most medical color photography.

4. No film available at present is sufficiently versatile to fulfill completely the requirements of medical photography. Each film has certain desirable properties.

5. Proper color is attained when the light source and the film type are compatible.

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Books Received

Books received are acknowledged by listing. As space permits, selected books are reviewed more extensively. Reviews in this issue start on page A-142; additional listings appear on page A-146.

Manual of Clinical Bacteriology. By Alexander Kimler, Ph.D., Division of Research Services, National Institutes of Health, Bethesda, Maryland. 201 pages, illustrated. 1961, J. B. Lippincott Company, Philadelphia and Montreal. $4.75.

Adrenergic Mechanisms. Ciba Foundation Symposium. Edited by J. R. Vane, D.Phil., Department of Pharmacology, Royal College of Surgeons of England, G. E. W. Wolstenholme, O.B.E. and Maeve O'Connor, B.A., London, England. 632 pages with 163 illustrations. 1961, Little, Brown & Company, Boston. $12.50.

The Closed Treatment of Common Fractures. By John Charnley, F.R.C.S., Orthopaedic Surgeon, Manchester Royal Infirmary, Manchester, England. Ed. 3. 272 pages, illustrated. 1961, The Williams & Wilkins Company, Baltimore. $10.00.

Traumatic Lesions of Peripheral Vessels. By Carl W. Hughes, M.D., Chief, General Surgery Service, and Warner F. Bowers, M.D., Chief, Department of Surgery, Tripler Army Hospital, Honolulu, Hawaii. 197 pages, illustrated. 1961, Charles C Thomas, Springfield, Illinois. $8.00.

Annals of the New York Academy of Sciences, 1961. Vitamin C. Vol. 92, Art. 1. 332 pages, illustrated.

Intra-Abdominal Crises. By Kenneth D. Keele, M.D., Consultant Physician, and Norman M. Matheson, F.R.C.S., Consultant Surgeon, Ashford Hospital (Staines Group), London, England. 397 pages with 68 illustrations. 1961, Butterworth Inc., Washington, D. C. $10.00.

The Cardiac Arrhythmias; a Guide for the General Practitioner. By Brendan Phibbs, M.D., Casper Clinic, Casper, Wyoming. 128 pages, illustrated. 1961, The C. V. Mosby Company, St. Louis. $7.50.

Illustrating Medicine and Surgery. By Margaret C. McLarty, D.A. (Edin.), United Oxford Hospitals, Oxford, England. 159 pages with 178 illustrations. 1960, The Williams & Wilkins Company, Baltimore. $8.50.

Hypokinetic Disease. Diseases produced by lack of exercise. By Hans Kraus, M.D., Associate Professor, Physical Medicine and Rehabilitation, New York University School of Medicine, New York, and Wilhelm Raab, M.D., Director, Cardiovascular Research Unit, University of Vermont College of Medicine, Burlington. 193 pages, illustrated. 1961, Charles C Thomas, Springfield, Illinois. $7.50.

Blood Platelets. Henry Ford Hospital International Symposium. Edited by Shirley A. Johnson, Ph.D., Raymond W. Monto, M.D., John W. Rebuck, M.D. and Robert C. Horn, Jr., M.D., Henry Ford Hospital, Detroit. 732 pages, illustrated. 1961, Little, Brown & Company, Boston. $18.50.

Essentials of Neurology. By John N. Walton, M.D., Neurologist, Newcastle General Hospital and Newcastle Regional Hospital Board, Newcastle upon Tyne, England. 422 pages with 12 illustrations. 1961, J. B. Lippincott Company, Philadelphia and Montreal. $6.75.

Inflammation and Diseases of Connective Tissue. A Hahnemann Symposium. Edited by Lewis C. Mills, M.D., Head, Section of Endocrinology and Metabolism, and John H. Moyer, M.D., Chairman, Department of Medicine, Hahnemann Medical College and Hospital, Philadelphia, with 148 contributors. 900 pages, illustrated. 1961, W. B. Saunders Company, Philadelphia and London. $16.00.

Editorials

Postgraduate Medicine

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SYLVIA COVET

PROGRESS IN MILITARY MEDICINE

THE annual report of Lieutenant General Leonard D. Heaton, Surgeon General of the United States Army for the fiscal year 1960, indicates the great progress that has been made in military medicine in the last few decades. The primary mission of the army medical service is to maintain the health of the army, thus conserving its fighting strength, and to prepare in time of peace for mobilization in war. General Heaton calls attention to the great changes that have resulted from the development of new weapons. These are instruments of war which not only can kill or incapacitate men but also can produce incredible numbers of casualties in a matter of minutes. Nowadays much attention is given to the study of nuclear weapons and to the training of the individual soldier in first aid and self-aid so that he may survive on a nuclear battlefield.

From the point of view of medical progress, the army medical service has expanded its capabilities in cardiac catheterization and open-heart surgery. Radioisotope clinics and pulmonary physiology testing are being extended in the treatment facilities. Outpatient clinics and services are being rehabilitated and improved. In the army, as elsewhere, equipment becomes obsolete and new equipment is constantly necessary.

Perhaps one of the greatest changes that have taken place has been the development of the residency training program. Whereas army physicians of the past were principally general practitioners, the army now has on active duty nearly 1500 board-certified and board-qualified medical officers in 28 different medical specialties.

General Heaton is especially proud of the Medicare program, which the army administers for all the uniformed services. In this program, medical care is obtained from civilian sources for dependents of personnel on active duty. It has become a substantial fringe benefit for all military personnel. General Heaton is convinced that it is an effective morale-building supplement to the medical care which is provided by military facilities.

During 1960 the daily noneffective rate among troops declined to a new record low. The health of our armed forces proved to be excellent. The report of the Surgeon General is a most interesting document, full of information as to standards of physical fitness, the

conditions which disqualify young men for entrance into the armed forces, and the types of research being carried on in various specialties. For instance, with the introduction of specific drug therapy and the development of new surgical technics for tuberculosis, the army now treats successfully and returns to active duty more than 90 per cent of soldiers either immediately after treatment or after temporary retirement. The relapse rate among men thus returned to service has been less than 2 per cent.

MORRIS FISHBEIN

WOMEN IN INDUSTRY

WOMEN are increasingly a component in the labor force in the United States. The proportion of women in industry rose from one-sixth of all workers in 1890 to one-fourth just before World War II, and is even higher at present. In 1960 one of every three workers (actually more than 22.5 million) was a woman. The majority of nutritionists, dietitians, librarians, nurses, stenographers, secretaries and telephone operators are women. Women also predominate among teachers, cashiers, bookkeepers, office-machine operators, and workers in the textile and tobacco industries. The number of persons in the professions has been growing faster than in other occupational groups; however, the proportion of women in the professions has declined since 1940, because the number of professional men has increased even faster. The average age of women workers has been increasing steadily since 1900 to a present level of just over 40 years.

These and many other interesting facts relating to women in industry have been published by Evelyn S. Spiro[1] as part of a symposium in the *American Journal of Public Health*. More than one-half of the women who work are married and live with their husbands. One of every 10 working women has preschool children, and one of three has children less than 18 years of age. Women are marrying younger, having more children, and having them earlier than they did before the second World War.

The medical profession is particularly concerned with the illness and absenteeism of women workers. In a survey made among workers in a leading oil company, women employees averaged more than twice as many absences as did men but stayed away from work only half as long. The average number of days lost because of sickness was 9.9 a year for women and 9.3 for men. Interestingly, the highest number of days lost from work because of illness or injury for both men and women occurred in the lowest income group. Apparently, when it costs more to stay away from work, there is less likelihood of absence. More and more emotional causes are beginning to play a part in absenteeism.

In another survey, Dr. L. E. Hinkle, Jr. and co-workers[2] have examined the relationship between symptoms, disability and serious illness in two homogeneous groups of men and women in industry. The women reported more episodes of illness than did the men, and the illnesses reported were bona fide. Excessive illnesses observed among women consisted almost entirely of colds, sore throats, acute gastroenteritis, dysmenorrhea, muscular pains, minor cuts and bruises, headaches, and minor disturbances of mood, thought and behavior. The authors believe that the men experienced an equal number of illnesses, and simply did not report them to the doctor and did not stay away from work because of them. Incidentally, the telephone operators, whose work is sedentary and almost wholly without exposure to injury, had more minor lacerations and bruises than did the men who install and repair telephone equipment. The investigators further observed that the only minor illnesses which occurred significantly more often among women than among men were minor episodes of tension, anxiety, asthenia and depression. It was concluded that women were more frequently disabled and disabled more of the time than men, but that they incurred less risk of death because of their illnesses. In this sense, the women were healthier than the men.

From these observations comes the conclusion that the higher incidence of illness reported by women, the greater amount of disability that they experienced, and the greater

number of visits that they made to the doctor were largely the results of culturally determined differences in the attitudes toward what constitutes illness and what creates an acceptable reason for disability in men and in women.

In a concluding article in this important series, Dr. Luella E. Nadelhoffer[3] has reviewed gynecologic problems and their effect on the working woman. Dr. Nadelhoffer believes that gynecologic problems can be minimized by an adequate pre-employment examination and health-maintenance program and by cooperation between the family doctor and the industrial physician. Pre-employment examinations should include examination of the breasts and pelvis. Women employees should be encouraged to have regular physical checkups, including breast and pelvic examinations, and a Papanicolaou smear of the cervix should be done at least once yearly. The chief gynecologic problems affecting the working woman are menstrual disorders, pelvic pain, vaginal discharge, infertility, the climacteric, relaxation of the pelvic floor, and pregnancy. Dr. Nadelhoffer noted that the psychologic factors involved in a pregnant woman's working are of special significance. Preferably, a pregnant woman should be in a position where she is not before the public and should count on 24 to 28 weeks as an optimal time for discontinuing employment.

A study of trends in employment indicates that the number of women employed is likely to increase rather than decrease. The medical and psychologic factors involved will undoubtedly require increasing study and consideration by public health and medical organizations in the years to come.

MORRIS FISHBEIN

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2. Hinkle, L. E., Jr., Redmont, R., Plummer, N. and Wolff, H. G.: Women in industry: II. An examination of the relation between symptoms, disability and serious illness in two homogeneous groups of men and women. *Ibid.*,[1] pp. 1327-1336.
3. Nadelhoffer, L. E.: Women in industry: III. Gynecological problems—their effect on the working woman. *Ibid.*,[1] pp. 1337-1341.

DOCTORS' CHOICE

At Columbia University School of Public Health and Administrative Medicine, Drs. Milton C. Maloney, Ray E. Trussell and Jack Elinson[1] have studied through personal interviews the question of the kind of doctor a physician selects when he or a member of his family needs medical service. The doctors queried were all practicing in New Jersey.

When asked if everyone should have his own personal physician, nine of 10 physicians said yes. Seven of 10 said that even physicians should have a personal physician. However, only two of five doctors said that they had a personal physician, and only one of five doctors had seen a physician for any reason in the previous year. The doctors chose as their personal physicians full-time specialists in internal medicine who are certified by the American Board of Internal Medicine and are fellows of the American College of Physicians. They usually had had long-standing professional and personal relationships with these internists.

In choosing a surgeon for either himself or a member of his family, the doctor usually selected a surgeon who is a diplomate of the American Board of Surgery and member of the American College of Surgeons. When the doctor went outside his community for service he selected a teacher working in the hospital or medical school and generally the chief of surgery. Not one doctor selected a general practitioner as a surgeon. The report stated that the surgeon ". . . is more frequently chosen for his reputation and less often for direct knowledge or appraisal of his technical competence than is his personal physician." Nine of 10 anesthetists who gave anesthetics to those undergoing surgery were physicians.

This study is part of a total study which will cover other aspects dealing with the quality of medical care.

MORRIS FISHBEIN

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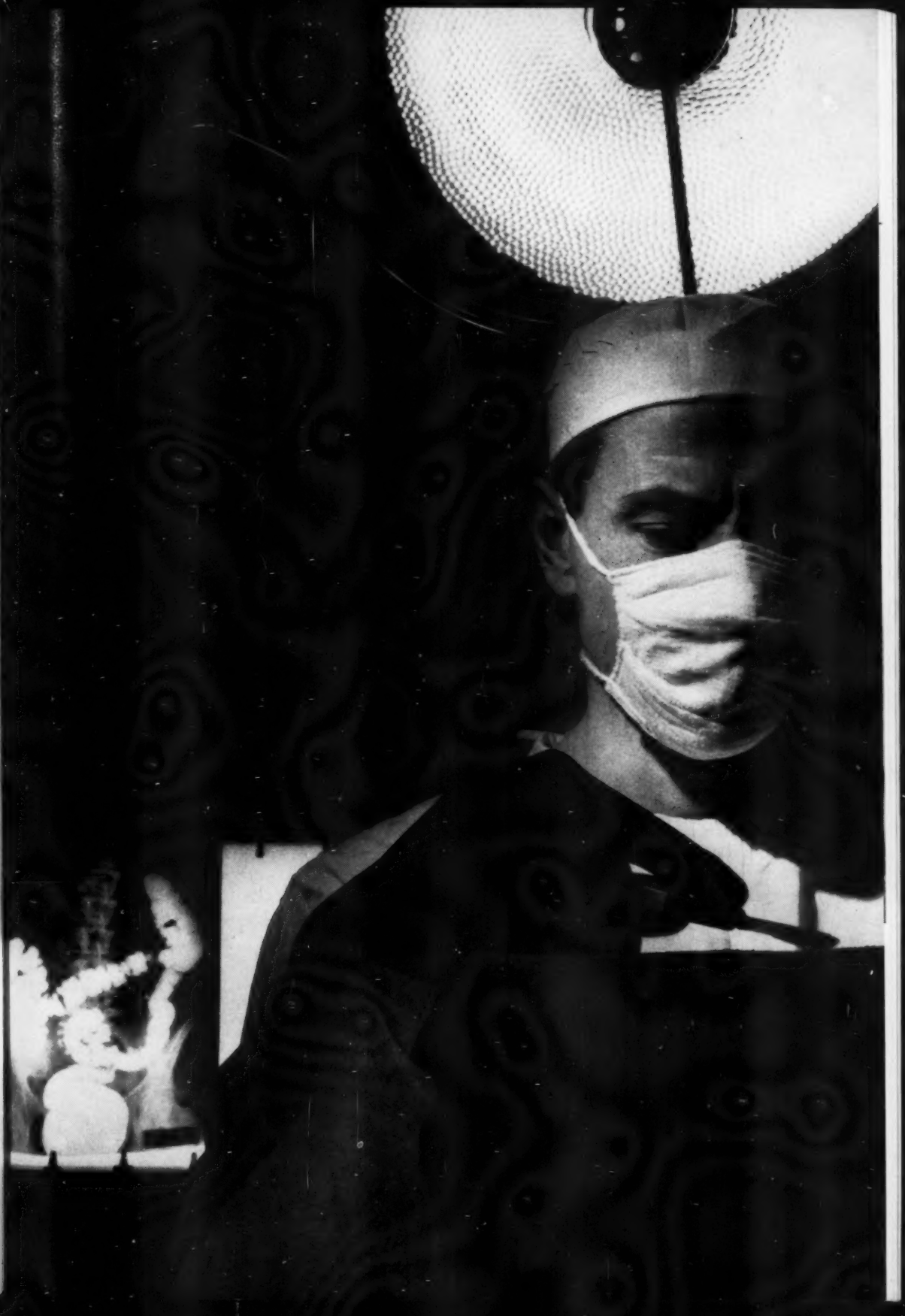

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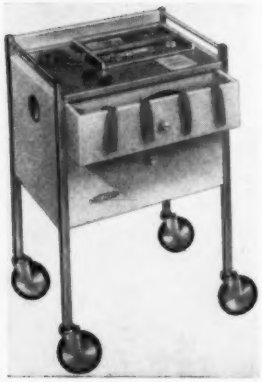

• CONSOLE ELECTROCARDIOGRAPH

DESCRIPTION: Constructed so that the electrocardiograph may be removed, this console model features a built-in retractable cord, large storage drawers, ample work space, oversize casters, and a plastic cover. The recording unit provides simplified paper loading, fine definition with a tubular stylus, fast switching from lead to lead, and both 25 and 50 mm. speeds.
PRODUCER: The Burdick Corporation, Milton, Wis.

• ANALEXIN®-400 (New Product Form)

PURPOSE: Analgesic therapy.
COMPOSITION: Each capsule contains 400 mg. phenyramidol hydrochloride.
DOSAGE AND ADMINISTRATION: 1 capsule at onset of pain, followed by 1 capsule at intervals of one to four hours as needed.
HOW SUPPLIED: Bottles of 50.
PRODUCER: Irwin, Neisler & Co., Decatur, Ill.

• BETA-L TEST

DESCRIPTION: A simple means of detecting elevated beta-lipoprotein levels in serum, this test provides accurate determinations in less than 10 minutes. Compact kits for 60 tests contain antiserum, capillary pipets, Immunocrit tubes, a magnifying viewer, millimeter scales and disposable slides.
PRODUCER: Hyland Laboratories, Los Angeles, Division of Baxter Laboratories, Inc., Morton Grove, Ill.

• FURACIN®-HC URETHRAL SUPPOSITORIES (New Product Form)

PURPOSE: To provide antibacterial, anti-inflammatory and anesthetic action in urethral conditions.
COMPOSITION: Each 1.3 gm. suppository contains 0.2 per cent Furacin, 1 per cent hydrocortisone acetate, and diperodon hydrochloride in a water-dispersible base.
DOSAGE AND ADMINISTRATION: 2 or 3 suppositories daily for four days.
HOW SUPPLIED: Boxes of 12.
PRODUCER: Eaton Laboratories, Division of The Norwich Pharmacal Company, Norwich, N. Y.

• MUCOPLEX®

PURPOSE: To treat abnormalities of the oral mucosa.
COMPOSITION: Each tablet contains:

HEPROFAX®	750 mg.
Vitamin B_{12} as Ionex-12	5 μg.
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DOSAGE AND ADMINISTRATION: 1 or 2 tablets three times a day or as directed.
HOW SUPPLIED: Bottles of 100 and 500.
PRODUCER: The Stuart Company, Pasadena.

(Continued on page A-104)

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DESCRIPTION: Upholstered in foam rubber and sand-colored Naugahyde, this commode chair doubles as a piece of contemporary furniture. It features a removable receptacle which is hidden when the chair cushion unit is in place; a high-gloss, waterproof white commode seat; stained walnut arms and legs; an innerspring back, and bolted construction.
PRODUCER: Everest & Jennings, Inc., Los Angeles.

• ANADROL®

PURPOSE: To stimulate weight gain and to halt tissue breakdown.
COMPOSITION: Each tablet contains 2.5 mg. oxymetholone.
CAUTION: Anadrol is contraindicated in carcinoma of the prostate, nephritis and nephrosis and should be used with caution in patients with known hepatic damage or heart disease. It should not be given to children for more than 30 days because of increased sensitivity to masculinizing effects. If such symptoms develop, administration should be discontinued.
DOSAGE AND ADMINISTRATION: For adults and children more than 12 years old, the usual dosage is 2.5 mg. three times a day. For children less than 12 years old, 2.5 mg. or 5 mg. a day will provide an adequate response.
HOW SUPPLIED: Bottles of 50.
PRODUCER: Syntex Laboratories, Inc., New York.

• QUANTI-VITE (F) PEDIATRIC DROPS

PURPOSE: Dietary supplement and prevention of dental caries.
COMPOSITION: Each 0.6 ml. provides six vitamins, 10 mg. niacinamide and 0.5 mg. fluorine (from 1.1 mg. sodium fluoride).
CAUTION: This preparation is contraindicated in communities with naturally or artificially fluoridated drinking water containing more than 0.3 part per million of fluorine.
DOSAGE AND ADMINISTRATION: 0.6 ml. daily, undiluted or mixed with fluids.
HOW SUPPLIED: 50 ml. bottles with calibrated droppers.
PRODUCER: Hoyt Pharmaceutical Corp., Newton, Mass.

• VŌSOL® HC OTIC SOLUTION

PURPOSE: For treating otitis externa.
COMPOSITION: This nonaqueous solution contains:

1,2-Propanediol diacetate	3%
Acetic acid	2%
Benzethonium chloride	0.02%
Hydrocortisone	1%

The agents are combined in a propylene glycol vehicle.
HOW SUPPLIED: 7.5 cc. measured-drop bottles.
PRODUCER: Wampole Laboratories, Stamford, Conn.

• MULVIDREN® DROPS
(New Product Form)

DESCRIPTION: This pediatric multivitamin preparation is supplied in 30 cc. bottles. The usual dose is 0.3 cc. for infants and 0.6 cc. for children.
PRODUCER: The Stuart Company, Pasadena.

• LIBRIUM® INJECTABLE
(New Product Form)

DESCRIPTION: For treating acute agitation and hyperactivity, this drug can be administered either intravenously or intramuscularly. Detailed directions, dosages and precautions are given in the package inserts. The drug is available in boxes of six and 25 duplex packages, each package providing a 5 cc. dry-filled ampule containing 100 mg. Librium hydrochloride in crystalline form and a 2 cc. ampule of a special diluent for intramuscular injection.
PRODUCER: Roche Laboratories, Division of Hoffmann-La Roche, Inc., Nutley, N. J.

• MALERICH STAND

DESCRIPTION: Constructed of stainless steel, this multipurpose stand may be used in a variety of treatment situations. The 23 lb. unit consists of a tray on an adjustable base, and it may be moved easily about the hospital.
PRODUCER: Wilson Manufacturing Company, Columbus, Ga.

(Continued on page A-106)

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Sustained

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1 tablet all day

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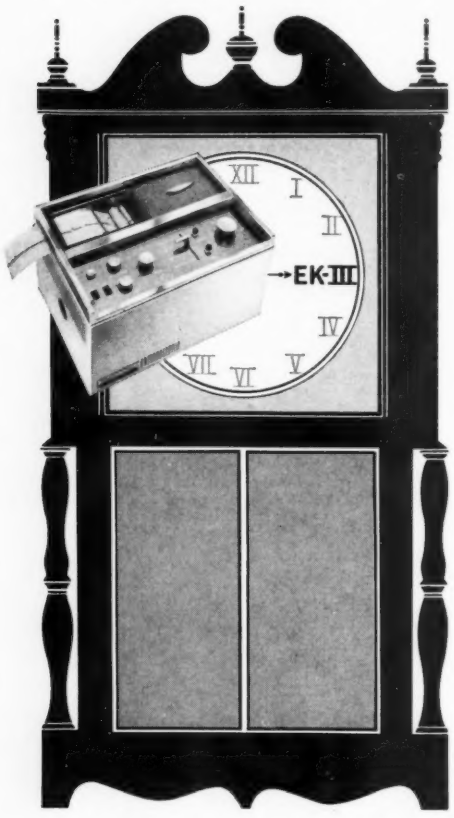

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Now is the time to trade up to Burdick!

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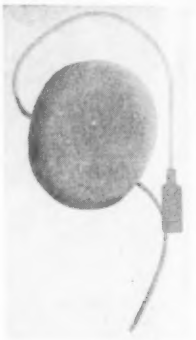

• IMPLANTABLE PACEMAKER

DESCRIPTION: Entirely sealed in a special plastic, this transistorized electronic pacemaker weighs less than 10 oz. The instrument is placed within the body, usually near the abdomen, and is connected to the heart by internal wires. It produces only a slight bulge and causes no discomfort.
PRODUCER: Medtronic, Inc., Minneapolis.

• FERROLIP®-T

PURPOSE: Dietary supplement.
COMPOSITION: This product contains iron choline citrate chelate and vitamins B_1, B_6 and B_{12}.
PRODUCER: Flint-Eaton & Co., Division of Baxter Laboratories, Inc., Morton Grove, Ill.

• HYDROCORTISONE (1%) AND COR-D-TAR CREAMS

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CAUTION: These creams are contraindicated in tuberculosis of the skin. Adequate therapeutic measures should be instituted to control unresponsive organisms.
DOSAGE AND ADMINISTRATION: A small quantity applied to affected skin two or three times daily.
HOW SUPPLIED: ½ and 1 oz. tubes.
PRODUCER: Desitin Chemical Company, Providence.

• FERTILITY TESTOR

DESCRIPTION: For predicting the fertile phase of the menstrual cycle, this fertility testing tape assays the glucose content of the cervicouterine and tubal fluid. The tape employs a double-enzyme system of glucose oxidase and a peroxidase. Fixed to the end of a plastic rod in a narrow plastic vaginal barrel, the tape is brought into contact with the cervix for three minutes; the rod is then withdrawn through the protective barrel. Color reaction is blue if the patient is in a fertile period of her cycle.
PRODUCER: Weston Laboratories, Inc., Ottawa, Ill.

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Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets; bottles of 50. Also as MEPROTABS*— 400 mg. *unmarked,* coated tablets; and in *sustained-release* capsules as MEPROSPAN®-400 and MEPROSPAN®-200 (containing respectively 400 mg. and 200 mg. meprobamate).

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Great Names in American Medical History

Montana

Ferdinand R. Schemm, M.D.

This is one of a series of biographic sketches of outstanding physicians of the past from each of the 50 states. The subjects have been selected by the medical society of each state or its designated committee.

DR. Ferdinand Ripley Schemm was born in Saginaw, Michigan, June 12, 1899. He received an A.B. degree in 1923 and an M.D. degree in 1925, both from the University of Michigan. An internship and a residency in surgery at the University Hospital followed. After three years of private practice in Bay City, Michigan, and a year of postgraduate study in Europe, he returned to the University of Michigan Medical School as a teaching fellow in medicine. In 1933 he joined the Great Falls Clinic, where, in addition to a heavy clinical practice in internal medicine, he immediately began to do research without any of the advantages of a university center.

For 20 years, Dr. Schemm was in the fore among physicians who have advanced our knowledge of the pathogenesis and treatment of edema. He was largely responsible for the general acceptance of a more liberal intake of water in patients with edema. His first major publications in the field of water and electrolyte balance were published in the December issues of *Annals of Internal Medicine* in 1942 and 1944. His work clarified our concepts of dehydration. He was intensely interested in the present concept of lower nephron nephrosis and, as Dr. Newberg had shown previously, Dr. Schemm pointed out that kidneys, even in the face of severe toxic injury, remain able to excrete urine of low specific gravity and solids if allowed enough water to compensate for decreased renal concentrating capacity. He applied this general principle to the treatment of portal cirrhosis, edema during pregnancy, and degenerative vascular disease in diabetic patients. His last contribution was the study of the beneficial effect of corticotropin in resistant heart failure with or without edema.

Dr. Schemm served in the department of internal medicine of the Great Falls Clinic for many years, and was director of the Metabolic Unit for Cardiovascular Disease, Western Foundation for Clinical Research, Montana Deaconess Hospital. During World War I, he served in the Second Army Ambulance Corps; in World War II, he was consultant in internal medicine, Montana Selective Service Board. He was a diplomate of the National Board of Medical Examiners and of the American Board of Internal Medicine, certified in the subspecialty of cardiovascular diseases. In 1950 he was invited to address a meeting of the International College of Cardiologists in Paris.

Dr. Schemm died May 16, 1955.

YOUR FINANCES

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Narrowing the selection of an investment fund . . . specific performance records of some leading funds . . . how they compare with the general market.

prepared by

CEDRIC CAMPBELL

for

Postgraduate Medicine

September 1961

With your own investment objectives as a starting point, review the type of fund that most closely matches your aims. Then narrow down the likely candidates on the basis of actual performance. After all, you'll be paying for professional management; why not buy the best?

For purposes of comparison and evaluation, let us examine some specific records during a recent five-year period (to 1959) during which the Dow-Jones Industrial Average rose 73%.

Conservative funds (taking only those with total assets over $100 million) producing an income of 3% or better included Axe Houghton Fund B, Commonwealth Investment Co., Easton & Howard Balanced Fund, Investors Mutual, Putnam Fund of Boston, Wellington Fund. In the same period, these funds enjoyed a growth in net asset value (including income return) averaging 38%.

Income funds with total assets in excess of $75 million that produced income of 3.5% or more included Incorporated Income Fund, National Securities Dividend Series, United Income Fund, Keystone Custodian Fund S-2, Puritan Fund. Growth averaged 45.3% for these funds.

Among more speculative funds reporting outstanding capital appreciation in the same period were Diversified Growth Stock Fund (106%), Dreyfus Fund (115%), Founders Mutual (86%), Keystone Custodian (98%), Massachusetts Investors Growth Stock Fund (91%), National Investors Corp. (90%).

* * * * *

Where tax benefits are a prime consideration, funds especially set up to fill this requirement should be fully explored. A small number of funds offer a tax shelter because they have incurred capital losses on earlier stock purchases. Bear in mind that the benefits to be derived will vary with the individual's own situation.

Non-Resident-Owned Canadian Funds may provide an attractive, favored tax position for investors in higher tax brackets. Ownership of these funds is at least 95% non-Canadian, but they are incorporated

and operated in Canada. The fund is not taxed by the U. S. and, due to its "foreign" ownership, is given favored tax treatment by the Canadian government. The fund may choose either to pay 15% on all income it received (dividends, interest, etc.), or to pay at the regular Canadian corporate tax rate which is levied only on income other than dividends received from Canadian companies.

In addition, N-R-O Canadian Funds pay no tax on realized capital gains, which may be reinvested in their entirety.

As a U. S. citizen you will pay taxes on your N-R-O fund shares only when you dispose of these shares. Appreciation in the value of these shares will then be taxable as a capital gain. In other words, you choose when you want to take your profits—and pay your taxes.

Among the N-R-O Canadian Funds, consider candidates such as Canada General Fund, Canadian International Growth Fund, Axe-Templeton Growth Fund of Canada, Keystone Fund of Canada, United Funds of Canada. Your selection should, of course, meet all your other standards as to portfolio, objectives, management, and record of performance.

Bermuda-based funds provide additional avenues for investments with favored tax treatment. Here again, tax laws permit nonresident funds to pay virtually no taxes on capital gains, with only modest levies on income. If the fund reinvests both income and capital gains (which these funds are not obligated to distribute), capital appreciation over a longer period of time can be substantial. As in the case of the N-R-O Canadian Funds, capital gains taxes apply for U. S. investors only when shares are sold.

* * * * *

Newest in tax-shelter funds—Small business investment companies. Started in 1958 by virtue of the government's Small Business Investment Act, they have grown in number to the hundreds. Their purpose was to provide a source of capital for the smaller business through long-term loans and the purchase of debentures convertible into common stock.

Any capital gains realized by the SBIC's are taxed at capital gains rates. Additional tax advantages permit the investment company to take a 100% deduction on capital losses suffered on its holdings. Shareholders, in turn, may treat any losses they suffer on SBIC stock in the same manner.

Caution: Since the small business investment companies specialize in supplying venture capital to small, new enterprises, these shares must be considered only where speculative holdings are sought. Percentages simply do not favor the majority of young ventures and the mortality rate is high. However, as a fully calculated risk, these funds provide a means of participating in the fortunes of a number of young businesses, some of which may conceivably grow at a very rapid rate.

Consider some of the old timers in this group including Venture Capital Corp., Texas Capital Corp., Electronics Capital Corp., Boston Capital Corp., Florida Capital Corp., Growth Capital, Inc.

* * * * *

'Tax-free' exchange funds should interest only those investors of means who are holding stocks with substantial unrealized gains. For example: You bought 1,000 shares of XYZ at $10 per share, for a total investment of $10,000. Present market price is $25. You may choose to exchange these shares for $25,000 worth of shares in an "exchange fund" and not pay any tax on the transaction. You have thus taken your $15,000 gain at no immediate tax cost, and diversified your investment by trading for shares in the investment fund. Longer-term tax factors, the portfolio of the fund, its management and other considerations should be weighed and your own position as an exchange fund shareholder should be fully understood before completing the transaction. An increasing number of these funds are being started, and your dealer will inform you of the shares available and provide full details.

* * * * *

The latest trend in mutual funds is toward funds whose primary objective is capital gains, with income a secondary consideration. So far in 1961, 51% of all new investments in fund shares have been put into 20 of the leading growth funds. This percentage compares with the 34% invested in this type of fund in 1960.

* * * * *

Shares of closed-end investment companies—especially those that enjoy broad diversification—also warrant the investor's investigation.

During the 5-year period used in the performance analysis of mutual funds, impressive records were turned in by Adams Express Co. (growth including yield, 87%), American International Corp. (72%), Consolidated Investment Trust (70%), General Public Service (66%), Lehman Corp. (57%), Niagara Share (123%), Tri-Continental (73%).

Closed-end funds also offer bonds and preferreds shares—many enjoying a good record of interest and dividend payments without interruption.

* * * * *

When considering buying any investment company shares, bear in mind that . . . Your investment should be regarded as essentially a long-term commitment . . . You can take a 4% tax credit on all dividend income (but not capital gains) from fund shares, as long as the fund meets government requirements that 75% of its earnings is from stock dividends . . . Government regulations and tax treatment accorded

investments do change; find out what they are at the time you buy . . . A fund is as safe or speculative as the shares in its portfolio . . . If your fund holds common stocks, its own value will fluctuate with market trends . . . While earnings records have generally been good to date, there is no guarantee that at the time you wish to dispose of your fund shares, you will get back your original investment, especially if the market has drifted lower than when you acquired your shares.

* * * * *

IN THE NEXT ISSUE: Real Estate For The Neophyte, a discussion of opportunities open to the individual investor to participate in real estate income and capital appreciation.

* * * * *

Additional reading on material covered in this article might include: "Investment Companies," Arthur Weisenberger & Co.; "Your Buying Guide To Mutual Funds and Investment Companies," Leo Barnes, American Research Council, and "Mutual Fund Directory," Investment Dealers' Digest, New York.

Information contained in these articles is as accurate as careful checking and reliable sources can make it, but cannot, of course, be guaranteed.

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THE MEDICAL Bookman

► THE YEAR BOOK OF ENDOCRINOLOGY (1960-1961)

Edited by Gilbert S. Gordan, M.D., Chief of Endocrine Clinics, University of California School of Medicine, Berkeley-San Francisco. 408 pages with 69 illustrations. 1961, Year Book Medical Publishers, Inc., Chicago. $8.00.

For anyone interested in endocrinology, this yearbook continues to be a valuable and essential volume. As in the past, it presents abstracts of recent pertinent endocrinologic literature and includes sections on the pituitary, parathyroids, thyroid, carbohydrate metabolism, adrenals and reproductive system. There also is an important section on endocrine influences in neoplastic disease. The current edition contains two special articles. One is a review of endocrinology in the Soviet periodicals published during 1959 and 1960, and the other is a provocative article entitled "What is a cretin?"

Dr. Gordan again has provided a stimulating introduction which reviews highlights in recent endocrinologic progress. He also has enhanced the text with his excellent editorial comments.

R. V. R.

► MANAGEMENT OF FRACTURES, DISLOCATIONS AND SPRAINS

By H. Earle Conwell, M.D., Associate Professor of Orthopedic Surgery, Medical College of Alabama, Birmingham, and Fred C. Reynolds, M.D., Professor of Orthopedic Surgery, Washington University School of Medicine, St. Louis. Ed. 7. 1,153 pages with 1,227 illustrations. 1961, The C. V. Mosby Company, St. Louis. $27.00.

The present edition of this widely accepted and much-respected book maintains the high level of accomplishment of the previous editions. Although no attempt is made to supply a catalogue of all injuries and their treatment, the text is surprisingly extensive. The authors tend toward conservative management of fractures. This edition also includes chapters on anesthesia for the injured person and a chapter on fractures of the jaw and related facial bones. The chapter on injuries of the hand has been brought up to date by Dr. Stein of Washington University School of Medicine.

As in the previous editions, the illustrations are exceptional; they have been wisely selected to portray the authors' ideas and to demonstrate the text. The index is complete, and the table of contents provides ready reference to the subject matter. Bibliographic references are included in the text rather than in a separate section of the book or at the end of each chapter.

E. W. J.

► ADVANCES IN BLOOD GROUPING

By Alexander S. Wiener, M.D., Senior Bacteriologist (Serology), Office of the Chief Medical Examiner, New York. 549 pages, illustrated. 1961, Grune & Stratton, Inc., New York and London. $11.00.

Except for a few papers included for historical interest, this book is a collection of articles by Dr. Wiener published since 1954. The papers deal chiefly with the technical aspects of Rh and ABO blood grouping, and the reader will find them difficult unless he has a firm basic knowledge in this field and an understanding of the Wiener Rh-Hr nomenclature. The controversy over the Rh-Hr and CDE systems of nomenclature is mentioned frequently, and five papers and three comments deal chiefly with this subject.

The sections on ABO blood groups and Rh-Hr blood types will be of special interest to those

(Continued on page A-144)

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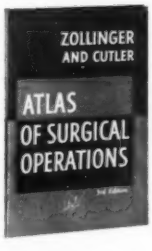

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involved in blood banking and related fields. Pediatricians and obstetricians will be interested in the papers on hemolytic disease of the newborn and exchange transfusions, and the information in the articles on the medicolegal application of blood grouping is essential to those in forensic pathology.

The basic concept of a collection of reprints on a specific subject is excellent and should be encouraged in other fields. This approach allows a critical evaluation of the author's methods, controls, results and conclusions. The only criticisms of this book are that its nature limits the material to those subjects on which the author has written papers and that only one viewpoint on an often controversial subject is presented. However, this last objection is largely erased by Dr. Wiener's pre-eminence and his vast experience.

F. A. F.

► DISEASE AND INJURY

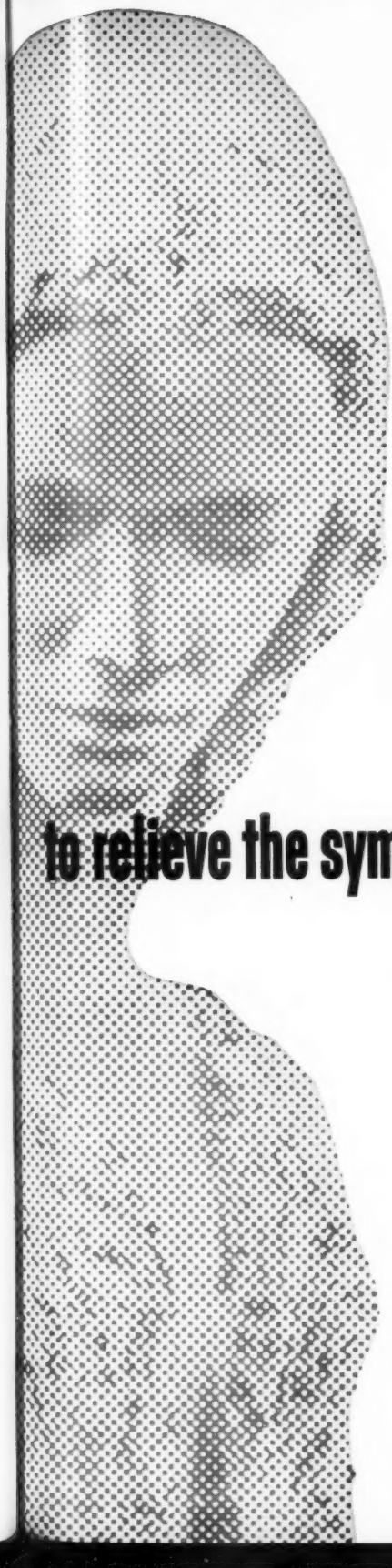
Edited by Leopold Brahdy, M.D., Formerly, Physician-in-Charge, Occupational Diseases and Injuries, City of New York, with 25 contributors. 482 pages, illustrated. 1961, J. B. Lippincott Company, Philadelphia and Montreal. $12.50.

Anyone who has been confronted with the problem of determining what causal relation, if any, a given injury may have had to a given disease is well aware of how difficult it may be to find the answer in the usual sources of information. This volume is a laudable attempt to bring together a large amount of information concerning the relation of injury to various diseases which usually arise without injury.

Following an introductory chapter devoted to general concepts concerning the relations between injury and disease, there are chapters dealing with the role of injury in the etiology of diabetes; neoplasms; heart, peripheral vascular, pulmonary, gastrointestinal, genitourinary tract, obstetric and gynecologic, joint, and thyroid diseases; and diseases of the nervous and skeletal systems. It is obvious that in many instances, such as exophthalmic goiter, the relation between injury and disease is still nebulous. Nevertheless, the existing evidence in all instances is well presented by the various contributors, and extensive references at the end of each chapter support the conclusions in the text.

R. V. R.

(Continued on page A-146)



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Books received are acknowledged by listing. As space permits, selected books are reviewed more extensively. Additional listings appear on page 279.

Multiple Sclerosis: Prognosis and Treatment. American Lecture Series. By Leo Alexander, M.D., Director, Multiple Sclerosis Research Clinic and Neurobiologic Unit, Division of Psychiatric Research, Boston State Hospital, Austin W. Berkeley, Ph.D., Professor of Psychology, Boston University, and Alene M. Alexander, Administrative Assistant, Multiple Sclerosis Research Clinic, Boston State Hospital, Boston. 188 pages, illustrated. 1961, Charles C Thomas, Springfield, Illinois. $7.50.

A Synopsis of Ophthalmology. By J. L. C. Martin-Doyle, M.R.C.S., Senior Surgeon, Worcester Eye Hospital, Worcester, England. Ed. 2. 249 pages, illustrated. 1961, John Wright & Sons Ltd., Bristol, England. Distributed by The Williams & Wilkins Company, Baltimore. $6.50.

The Human Cerebellum. An atlas of gross topography in serial sections. By Jay B. Angevine, Jr., Ph.D., Associate in Anatomy, Harvard Medical School, Elliott L. Mancall, M.D., Assistant Professor of Neurology, Jefferson Medical College, Philadelphia, and Paul I. Yakovlev, M.D., Clinical Professor of Neuropathology, Harvard Medical School, Boston. 138 pages, illustrated. 1961, Little, Brown & Company, Boston. $15.00.

Control of Ovulation. Proceedings of the conference held at Endicott House, Dedham, Massachusetts, 1960. Edited by Claude A. Villee, M.D., Department of Biological Chemistry, Harvard Medical School, Boston, with 33 contributors. 251 pages, illustrated. 1961, Pergamon Press Inc., New York. $10.00.

Listeriosis. By H. P. R. Seeliger, Dr. Med., Hygiene-Institut, Rheinische Friedrich-Wilhelms-Universität Medizinische Fakultat, Bonn, Germany. Ed. 2. 308 pages with 62 illustrations and five color plates. 1961, Hafner Publishing Company, Inc., New York. $14.25.

Clinical Disturbances of Renal Function. By Abraham G. White, M.D., Chief, Renal Disease Clinic, Queens Hospital Center, Jamaica, New York. 468 pages, illustrated. 1961, W. B. Saunders Company, Philadelphia and London. $10.50.

The Human Adrenal Gland. By Louis J. Soffer, M.D., Head of Endocrinology, Mount Sinai Hospital, New York, Ralph I. Dorfman, Ph.D., Director of Laboratories, Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts, and J. Lester Gabrilove, M.D., Associate Attending Physician, Mount Sinai Hospital, New York. 591 pages with 79 illustrations and one color plate. 1961, Lea & Febiger, Philadelphia. $18.50.

British Medical Bulletin. Foetal and Neonatal Physiology. Symposium prepared by 22 contributors. Vol. 17. No. 2. 98 pages, illustrated. 1961, Medical Department, The British Council, London. $3.25.

The Medical Muse

RICHARD ARMOUR

NOTE TO DERMATOLOGISTS

Long Island University scientists have discovered that perfume oils kill bacteria and fungi, both for the person who wears the perfume and the one who inhales it.—*News item.*

The perfume worn by Jane or Nancy
Does more than merely stir the fancy,
Does more, indeed, with its aroma,
Than leave men in a helpless coma.

Bacteria and fungi squirm
No longer on the epiderm
That's daubed or sprayed or doused quite well
With scents of Lanvin or Chanel.

Tell patients: Sniff her if you wish,
Or even kiss her (lovely dish);
You'll get the thrill that you'd expected,
And, what is more, be disinfected.

FOR OLD GOATS AND OTHERS

Goats suffering from the hereditary neuromuscular disease of myotonia are found to be relieved of their symptoms by depriving them of water. This may yield a clue to the treatment of the comparable disease in humans. —*News item.*

What works on goats may work on men
As thirsty as a blotter.
They, too, may be all well again
If they are kept from water.

Their muscular disease, if it's
Like that of goats, they say,
May, lacking water, stop its fits,
Dry up, and go away.

Then men who don't die on the spot
(The cure is rather risky)
Will have the reason they have sought
To live on gin or whisky.

restores
the will
to
improve

In Brief Niamid, brand of nialamide, is 1-(2-[benzylcarbamyl] ethyl)-2-isonicotinylhydrazine, a well-tolerated antidepressant that may correct or relieve depression on once-a-day dosage. **Indications:** Depressive syndromes of varying degrees of severity may be responsive to Niamid including: involutional melancholia, postpartum depression, depressed phase of manic-depressive reaction, senile depression, reactive depression, schizophrenic reaction with depressive component, psychoneurotic depression. ■ In neurotic or psychotic patients, Niamid may normalize or favorably modify aberrant or excessive reactions and symptoms of depression such as: phobias, guilt feelings, dejection, feeling of inadequacy, discouragement, worry, uneasiness, distrustfulness, hypochondriacal and nihilistic ideas, difficulty in concentration, insomnia, loss of energy or drive, indecision, hopelessness, helplessness, decreased functional activity, emotional and physical fatigue, irritableness, inability to rest or relax, sadness, anorexia and weight loss, and withdrawal from society. *In the withdrawn patient,* Niamid may elevate the mood so that there is increased activity, increased awareness and interest in surroundings, and increased participation in group activities. Appetite may be increased and there may be decreased fatigability. Lack of clinical response to other antidepressant therapy does not preclude a favorable response to Niamid. Relief of depression may also be evidenced by elimination or reduction of the need for somatic therapy, such as electroshock. *In patients suffering from depression associated with chronic illness,* Niamid may improve mental outlook, reduce the impact of pain, decrease the amounts of narcotics or analgesics needed, and improve appetite and well-being. *In patients with angina pectoris,* Niamid has been found to be a useful adjunct to management through reduction in frequency of attacks and pain. **Dosage:** Starting dosage is 75 to 100 mg. on a once-a-day or divided daily basis. This may subsequently be adjusted depending upon the tolerance and response. Responses to Niamid are not usually rapid, and revisions of dose should be withheld until at least a few days have elapsed at each level. Increments or decrements of 12½-25 mg. are generally sufficient. A daily dosage of 200 mg. is the maximum recommended for routine use. (As much as 450 mg. daily has been used in some patients.) **Side Effects:** Niamid, in clinical use, has been characterized by a significant lack of toxicity. It is generally well tolerated. Nervousness, restlessness, insomnia, hypomania, or mania, sometimes occur. Occasional headache, weakness, lethargy, vertigo, dryness of the mouth, blurred vision, increased perspiration, constipation, mild skin rash, mild leukopenia, and epigastric distress may be obviated or modified by reductions in dose. Effects due to monoamine oxidase inhibition persist for a substantial period following discontinuation of the drug. **Precautions and Contraindications:** Hepatic toxicity has not been reported in extensive clinical studies. However, if previous or concurrent liver disease is suspected, the possibility of hepatic reactions and liver function studies should be considered. ■ The suicidal patient is always in danger, and great care must be exercised to maintain all security precautions. The apathetic patient may obtain sufficient energy to harm himself before his depression has been fully alleviated. ■ Niamid may potentiate sedatives, narcotics, hypnotics, analgesics, muscle relaxants, sympathomimetic agents, thiazide compounds and stimulants, including alcohol. Caution should be exercised when rauwolfia compounds and Niamid are administered simultaneously. Rare instances have been reported of reactions (including atropine-like effects, and muscular rigidity) occurring when imipramine was administered during or shortly after treatment with certain other drugs that inhibit monoamine oxidase. **In Cardiology:** The central effects of Niamid may encourage hyperactivity and the patient should be closely observed for any such manifestation. Orthostatic hypotension or hypertensive episodes occur in a few individuals; cardiac patients should be carefully selected and closely supervised. **In Epilepsy:** Although in some patients therapeutic benefits have been achieved with Niamid, in others the disease has been aggravated. Care should be exercised in the concomitant use of imipramine, since such treatment with monoamine oxidase inhibitors has been reported to aggravate the grand mal seizures. **In Tuberculosis:** Existing data do not indicate whether resistance of M. tuberculosis to isoniazid may be induced with Niamid therapy; nevertheless, it should be withheld in the depressed patient with coexisting tuberculosis who may need isoniazid. ■ As with all therapeutic agents excreted in part via the kidney, due caution in adjusting dosage in patients with impaired renal function should be observed. **Supplied:** Niamid (Nialamide) Tablets, 25 mg.: 100's—pink, scored tablets; 100 mg.: 100's—orange, scored tablets./*More detailed professional information available on request.*

DR. Pepys' Pages

Personal Diary
and Observations on
Medical Life
by MORRIS FISHBEIN, M.D.

July 1—By the early plane to Elmira, where came Shallenberger, formerly of Chicago, to drive to Sayre, Pennsylvania, for a conference with alumni of the Guthrie Clinic and the Robert Packer Hospital. So with Bill Beck, the surgeon, to visit the convalescing Francis Brown. To dinner came a great multitude, with M. W. Norton of New Rochelle presiding, and the awards by S. D. Conklin to interns and residents for their work. Old Pepys spoke of medical progress and the prospect for the future, this being the third annual Donald Guthrie Memorial Lecture.

July 2—With Dr. J. T. Littleton driving to Binghamton, and from there to Pittsburgh and by jet to Idlewild. In the evening with the Friedells and Arthur Kline of Vienna to dine at Phil Schmit's.

July 3—All this day at the desk and reading a McBain mystery entitled "Give the Boys a Great Big Hand." In the afternoon with Arthur Kline and Friedell to play at golf, and in the evening to celebrate the Friedells' twentieth wedding anniversary.

July 5—To the final meeting of the Council on Public Education of the Chicago Heart Association, with Mark Lepper presiding, and excellent reports of our progress.

July 7—Now 47 years married to Mistress Pepys, so the day celebrated again at the golf course. Reading now a work by Robert Cunningham called "Hospitals, Doctors and Dollars," in which he accumulates his writings of some several years in the periodical called *The Modern Hospital*, and the book is filled out with several chapters dealing with such personalities as old Pepys, Charles Wilinsky and Arthur Bachmeyer.

July 8—At noon came Walter Kahoe and his lady from Philadelphia, and after luncheon to the Museum of Science and Industry, where are displayed some 50 photographs of the best work of Max Broedel. Then in the evening to a sixtieth birthday party for Manuel Smerling, and some 300 guests assembled to honor his important day. At the table with old Pepys and his lady were the Altschulers; the Salks, he being uncle to the famous Jonas; and the Schoenstadts of the Piccadilly Theatre.

July 9—At noon came Walter Kahoe with his lady to luncheon after the Quaker meeting, and with them to the Pump Room of the Ambassador to reminisce about England in the early 1800s. Then driving to the home of Dr. Greenberg in Glencoe where was a reception for Dr. Kushner, who becomes now chief of medicine in the Cook County Hospital, succeeding the late Howard Armstrong. Here were all of the attending staff and the educationalists of the area, including Sam Hoffman, Paul Szanto, Karl Meyer, Mrs. Dan Ryan, the Hertwigs, the Friedells, the Nechtows, and many of the youngsters.

July 10—All the day at the desk and in the evening to the Tavern Club, where came Larry Joselit and Helen, and here we met also the Maisons, Brenner and Service, with fine conversation and the telling of tales. After that, the evening being warm, to drive north through the parks and then back along the Outer Drive to our domicile.

July 11—Early to Don McNeill's program, which is now conducted while he is vacationing by Peter Donald. Later came Miss Pat Harris of the Lyric Opera to plan for further developments, and then in the evening to play at golf, finding it altogether enjoyable, particularly riding in the new cart.

July 12—Early came Bill Kaufman to plan further for the "Salute to Medical Research," of which the chairman this year will be Charles Walgreen. In the evening with Mistress Pepys to visit Maximilian Kern and his daughter Janet, enjoying a gorgeous meal which she herself prepared. So much talk of her new book, which will be published by Lippincott, and of literary, theatrical and TV life.

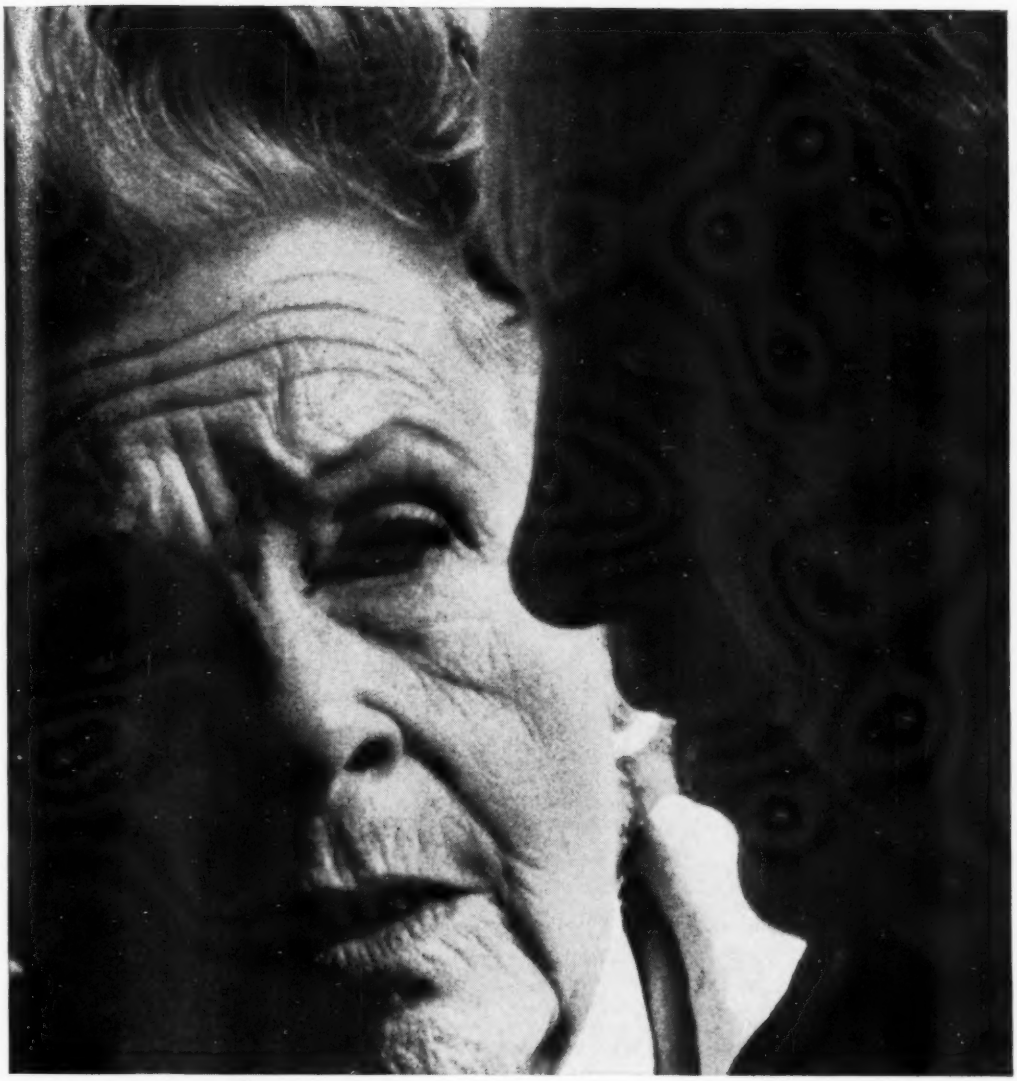
July 13—To the country club, where came also the Fred Hertwigs, Samuel Hoffmans, Walter Wrights and Friedells. Reading now the somewhat bitter essays of James Baldwin under the title "Nobody Knows My Name," and admiring especially the directness and quality of his scrivening. At the same time reading "Ippolita," an Italian novel of Corsica, with wonderful humor and insight, but apparently not too good a translation.

July 14—To interview several public relations experts and found them disordered as to just what might be their functions in modern society, and this is probably the least standardized of any profession.

July 15—At the desk and in the afternoon observing the televised baseball game. In the evening to dine with Mistress Pepys and Mrs. Shavin at the Tavern and then to observe "La Dolce Vita," which is replete with artistry and exciting scenes of Rome and its vicinity, but apparently quite haphazard, or as the Bible would say, "without form and void." Then to CBS to appear with Irv Kupcinet on "At Random," along with author James Baldwin and Roland Cross, a medico who is son of the former health commissioner of the State of Illinois and who would organize so-called independent physicians, these being young men apparently dissatisfied with the status of organized medicine. Also present was a wonderful nun-physician, Sister Aquinas from the Tuberculosis Sanatorium in Hong Kong, telling of the great incidence of this disease among the refugees from Red China. There, too, were Professor Tannenbaum, the historian, and Professor Drobonsky, who would free the captive nations; the comedian Buddy Hackett; and Jane Kasner Ardmore, who is a ghost writer for Hollywood celebrities. The discussions ranged the gamut of international relations and included the nature of humor and medical statesmanship.

July 16—To the country club for a day of recreation. Reading now "Goodbye, Dr. Roch," by André Soubiran, finding it dull and without any bearing on what goes on in American institutions for the mentally disturbed, except perhaps in rare instances.

(Continued on page A-164)



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For 25% more of these needed nutrients: Carnation Instant can be mixed over-strength by adding ⅓ cup extra crystals per quart. This enriched nonfat milk is one-fourth richer in calcium, protein, and B-vitamins than ordinary nonfat milk. It tastes naturally delicious, with a richer flavor your patients will enjoy. And even mixed over-strength, it costs them only 12¢ a quart.

ANOTHER QUALITY PRODUCT OF CARNATION COMPANY, LOS ANGELES 36, CALIFORNIA

July 17—At noon came Albert Dorfman to speak of research needs and rheumatic fever and such like. In the evening with Mistress Pepys to a dinner arranged by Harry Weissman and his lovely lady in the Presidential Suite at the Pick-Congress, and this evolved to be a seventy-second birthday dinner for old Pepys, to which all the children and in-laws had been invited.

July 18—Reading now "Writers at Work," a series of interviews published by *The Paris Review*. In the evening with Joe Kirsner, Phil Winston and the ladies to the Tavern Club for dining and conversation until midnight.

July 19—A half-day of work and a half-day of golf, and reading now "A Shooting Star," by Wallace Stegner, which is full of psychologic insight into the habits of the idle rich, and who does not wish he were one of them?

July 20—In conference with Harry Scheer about a new plastic model of a heart which he has designed, and again at golf.

July 21—To participate with Don McNeill on his return from his holiday and with guest Renee Taylor, who has written about the Hunzas tribe of Asia, who live at a high altitude and who, it is told, reach the average age of 125 years. Next came Ken Arnolt to speak of new ventures in bookbinding. In the evening, this being the anniversary of Justin and Ann, all to Morton's to dine and then to see a movie of Greece called "Never on Sunday," which received a well-merited prize.

July 22—Old Pepys is now 72 years of age, so welcomed the Mantels of Indianapolis, and then to dine at a wonderful dinner which Ann Fishbein beautifully prepared for all the family. Then to Ravinia to hear Conductor Rosenstock, with Byron Janis as soloist.

July 23—All this day preparing for a journey, and in the midst of the preparation observing the White Sox again on a winning streak.

July 24—Came all the secretaries —Hauswald, Cunningham and Sabat —and most busy until off for O'Hare Field at 1:00 P.M. So on TWA departing late, and lost another hour circling Idlewild Field because of fog. At the field for cocktails with some Revlon friends and then off to Milan.

July 25—At Paris late and caught in five minutes a plane to Milan, leaving the baggage to come later. Milan is bustling with new buildings, and a subway in construction has burst the streets. So slept awhile and then to dine at Gianino's.

July 26—Visiting again the great cathedral and the Arcade and viewing art objects at Finzi's. Then off to Venezia, stopping at beautiful Lake Garda for lunch at Mayer's. In Venice to the Danieli, being graciously welcomed and dining on the roof. Then by boat to the Lido to dance. In the raffle Mistress Pepys won a gorgeous Salviati vase.

July 27—All the morning viewing again the Piazza San Marco, visiting the shops, and walking the streets to the Rialto bridge, and back by water taxi to luncheon on the Danieli roof. Next by car to Bologna and then to Montecatini, meeting Max Schuster and his charming lady, and also Bill Frohlich. Reading now "The Edge of Sadness," by O'Connor, who permits a priest to tell a wonderful story full of deeply moving philosophy.

July 28—Lay late reading and then drove to Florence, or Firenze, visiting the shops on the Ponte Vecchia, dining alfresco, and seeing in the square the statues of "David," "Neptune" and "The Rape of the Sabines." Thereafter to view the statues and sketches and other mementos of Michelangelo. In the evening back to Montecatini to dine with the Schusters and Bill Frohlich, and met also Meyer Weisgal of the Weizmann Institute in Israel.

July 29—Drove via Arezzo to Perugia, where came Romola Vicchi and Riccardo to lunch. Mistress Pepys looked at the sweaters of Luisa Spagnoli, whose factory is in Perugia. Then on to Rome and to the Hassler, where came Professor Marino-Zuco and his stately lady and the newly married Pizzettis to dine on the roof.

July 30—After dinner with Mistress Pepys walked to Doney's, and observed the passers-by who seem to be mostly young people on tours.

July 31—To luncheon in the Hassler Palm Room and then to the Leonardo da Vinci Airport, where *Signor* Marino is in charge. Here came the Marino-Zucos, the del Tortos and the Pizzettis to say *a rivederci*, since we return in a few weeks. So flew on to Istanbul, where the Hilton looks out on the Bosporus and the Golden Horn.

The Cost of Medical Care

Recently my doctor gave me a prescription under the theory that my blood pressure was up. In the cool of a summer evening, I drove to a right smart drugstore accompanied by my wife and teen-age daughter. While the prescription was being processed we three proceeded to buy:

DAUGHTER:

One lipstick	$ 1.50
One ball-point pen	.69
One notebook	.25
One movie magazine	.25

WIFE:

One jar "Madam somebody or other's tissue cream"	6.00
Two tubes toothpaste	1.49
One Glow Worm shampoo	2.00
One Red Lustre nail polish	1.00

ME:

One he-man deodorant	1.00
Three paperback "whodunits"	1.50
One *True Magazine*	.25
One electric razor	32.00
One prescription	6.50
Total	$54.43
Sales tax	2.18
TOTAL	$56.61

THOUGHTS WHILE DRIVING HOME: Damn Dr. "T" and his prescriptions. His prescription cost me $56.61. The cost of medical care comes high!

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A Few Extraordinary Facts

On April 25, 1955, Philip Yadzek ate 77 hamburgers at one sitting.

On April 27, 1546, William Foxley, potmaker for the mint in the Tower of London, fell asleep and so remained for 15 nights, in spite of efforts to attract his attention by pinching, burning and other drastic methods.

About 12,000 books are published each year in the United States. The one most frequently referred to is the telephone book.

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